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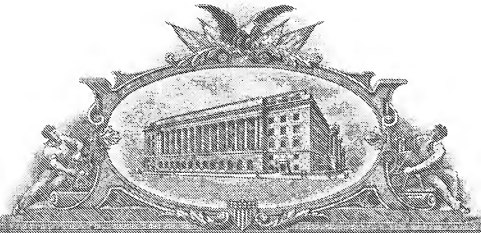

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APPLICATION NUMBER: *60/660,748*
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RELATED PCT APPLICATION NUMBER: *PCT/US06/07797*

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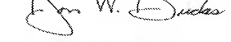

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Provisional Application of

DAVID W. OLD, et al.

March 10, 2005

For: SUBSTITUTED GAMMA LACTAMS AS THERAPEUTIC AGENTS

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

Mail Stop: Provisional Patent Application
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

1. The enclosed PROVISIONAL APPLICATION includes the following:

   1. Transmittal Letter – 2 pgs
   2. Specification (67pages) consisting of 9 Claims (2 pgs) Abstract (1 pg)
   3. Drawings (4 sheets)
   4. Declaration/Power of Attorney – 2 pgs.
   5. Copy of original Assignment with Recordation Cover Sheet – 4 pgs.
   6. Return/postage paid Postcard
   7. Express Mail Certificate No. EV295682112US

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3. Fee Payment

FOR	NUMBER FILED	NUMBER EXTRA	RATE	FEE
Provisional Application (Large entity)			$200.00	**$200.00**
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Please charge to Deposit Account No. 01-0885 for the filing fee of **$200.00**, as well as for any discrepancies that may occur.

4. Postcard Receipt

Applicants submit herewith a Return/Stamped Postcard.

Respectfully submitted,

Date: March 10, 2005

By: 

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CERTIFICATE OF EXPRESS MAIL UNDER 37 C.F.R. §1.10

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Date: March 10, 2005

Signature of person mailing paper

SUBSTITUTED GAMMA LACTAMS AS THERAPEUTIC AGENTS

By Inventors
David W. Old and Danny T. Dinh

DESCRIPTION OF RELATED ART

Ocular hypotensive agents are useful in the treatment of a number of various ocular hypertensive conditions, such as post-surgical and post-laser trabeculectomy ocular hypertensive episodes, glaucoma, and as presurgical adjuncts.

Glaucoma is a disease of the eye characterized by increased intraocular pressure. On the basis of its etiology, glaucoma has been classified as primary or secondary. For example, primary glaucoma in adults (congenital glaucoma) may be either open-angle or acute or chronic angle-closure. Secondary glaucoma results from pre-existing ocular diseases such as uveitis, intraocular tumor or an enlarged cataract.

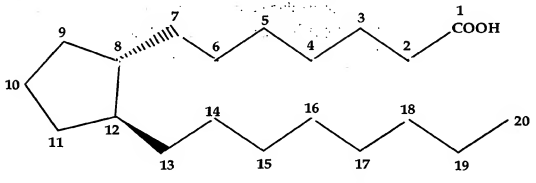
The underlying causes of primary glaucoma are not yet known. The increased intraocular tension is due to the obstruction of aqueous humor outflow. In chronic open-angle glaucoma, the anterior chamber and its anatomic structures appear normal, but drainage of the aqueous humor is impeded. In acute or chronic angle-closure glaucoma, the anterior chamber is shallow, the filtration angle is narrowed, and the iris may obstruct the trabecular meshwork at the entrance of the canal of Schlemm. Dilation of the pupil may push the root of the iris forward against the angle, and may produce pupilary block and thus precipitate an acute attack. Eyes with narrow anterior chamber angles are predisposed to acute angle-closure glaucoma attacks of various degrees of severity.

Secondary glaucoma is caused by any interference with the flow of aqueous humor from the posterior chamber into the anterior chamber and subsequently, into the canal of Schlemm. Inflammatory disease of the anterior

segment may prevent aqueous escape by causing complete posterior synechia in iris bombe, and may plug the drainage channel with exudates. Other common causes are intraocular tumors, enlarged cataracts, central retinal vein occlusion, trauma to the eye, operative procedures and intraocular hemorrhage.

Considering all types together, glaucoma occurs in about 2% of all persons over the age of 40 and may be asymptotic for years before progressing to rapid loss of vision. In cases where surgery is not indicated, topical β-adrenoreceptor antagonists have traditionally been the drugs of choice for treating glaucoma.

Certain eicosanoids and their derivatives are currently commercially available for use in glaucoma management. Eicosanoids and derivatives include numerous biologically important compounds such as prostaglandins and their derivatives. Prostaglandins can be described as derivatives of prostanoic acid which have the following structural formula:



Various types of prostaglandins are known, depending on the structure and substituents carried on the alicyclic ring of the prostanoic acid skeleton. Further classification is based on the number of unsaturated bonds in the side chain indicated by numerical subscripts after the generic type of prostaglandin [e.g. prostaglandin E_1 (PGE_1), prostaglandin E_2 (PGE_2)], and on the configuration of the substituents on the alicyclic ring indicated by α or β [e.g. prostaglandin $F_{2\alpha}$ ($PGF_{2\beta}$)].

Prostaglandin EP_2 selective agonists are believed to have several medical uses. For example, U.S. Patent No. 6,437,146 teaches the use of prostaglandin EP_2 selective agonists "for treating or preventing inflammation

and pain in joint and muscle (e.g., rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, juvenile arthritis, etc.), inflammatory skin condition (e.g., sunburn, burns, eczema, dermatitis, etc.), inflammatory eye condition (e.g., conjunctivitis, etc.), lung disorder in which inflammation is involved (e.g., asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.), condition of the gastrointestinal tract associated with inflammation (e.g., aphthous ulcer, Chrohn's disease, atrophic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.), gingivitis, inflammation, pain and tumescence after operation or injury, pyrexia, pain and other conditions associated with inflammation, allergic disease, systemic lupus crythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodose, rheumatic fever, Sjgren's syndrome, Behcet disease, thyroiditis, type I diabetes, diabetic complication (diabetic microangiopathy, diabetic retinopathy, diabetic neohropathy, etc.), nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Hodgkin's disease, Alzheimers disease, kidney dysfunction (nephritis, nephritic syndrome, etc.), liver dysfunction (hepatitis, cirrhosis, etc.), gastrointestinal dysfunction (diarrhea, inflammatory bowel disease, etc.) shock, bone disease characterized by abnormal bone metabolism such as osteoporosis (especially, postmenopausal osteoporosis), hypercalcemia, hyperparathyroidism, Paget's bone diseases, osteolysis, hypercalcemia of malignancy with or without bone metastases, rheumatoid arthritis, periodonritis, osteoarthritis, ostealgia, osteopenia, cancer cachexia, calculosis, lithiasis (especially, urolithiasis), solid carcinoma, mesangial proliferative glomerulonephritis, edema (e.g. cardiac edema, cerebral edema, etc.), hypertension such as malignant hypertension or the like, premenstrual tension, urinary calculus, oliguria such as the one caused by acute or chronic failure, hyperphosphaturia, or the like."

United State Patent No 6,710,072 teaches the use of EP2 agonists for the treatment or prevention of "osteoporosis, constipation, renal disorders, sexual dysfunction, baldness, diabetes, cancer and in disorder of immune regulation...various pathophysiological diseases including acute myocardial

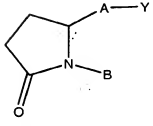
infarction, vascular thrombosis, hypertension, pulmonary hypertension, ischemic heart disease, congestive heart failure, and angina pectoris."

BRIEF DESCRIPTION OF THE DRAWING FIGURES

Figures 1-4 show examples of methods that can be used to prepare the compounds disclosed herein.

DESCRIPTION OF THE INVENTION

A compound is disclosed herein comprising

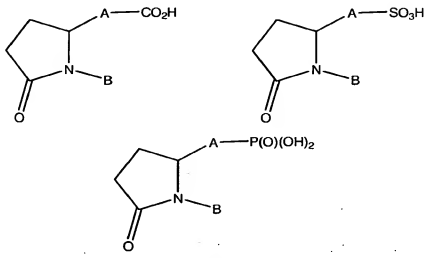


or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof; wherein Y is an organic acid functional group, or an amide or ester thereof comprising up to 12 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 12 carbon atoms; or Y is a tetrazolyl functional group; A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be substituted with S or O; or A is $-(CH_2)_m-Ar-(CH_2)_o-$ wherein Ar is interarylene or heterointerarylene, the sum of m and o is from 1 to 4, and wherein one CH_2 may be substituted with S or O; and B is aryl or heteroaryl.

Y is an organic acid functional group, or an amide or ester thereof comprising up to 12 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 12 carbon atoms; or Y is a tetrazolyl functional group.

An organic acid functional group is an acidic functional group on an organic molecule. While not intending to be limiting, organic acid functional groups may comprise an oxide of carbon, sulfur, or phosphorous. Thus, while not intending to limit the scope of the invention in any way, in certain

compounds Y is a carboxylic acid, sulfonic acid, or phosphonic acid functional group, i.e. one of the structures shown below.

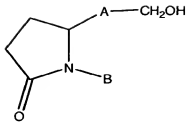


Salts of any of these acids of any pharmaceutically acceptable form are also contemplated.

Additionally, an amide or ester of one of the organic acids shown above comprising up to 12 carbon atoms is also contemplated. In an ester, a hydrocarbyl moiety replaces a hydrogen atom of an acid such as in a carboxylic acid ester, e.g. CO_2Me, CO_2Et, etc.

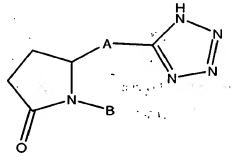
In an amide, an amine group replaces an OH of the acid. Examples of amides include $CON(R^2)_2$, $CON(OR^2)R^2$, $CON(CH_2CH_2OH)_2$, and $CONH(CH_2CH_2OH)$ where R^2 is independently H, C_1-C_6 alkyl, phenyl, or biphenyl. Moieties such as $CONHSO_2R^2$ are also amides of the carboxylic acid notwithstanding the fact that they may also be considered to be amides of the sulfonic acid R^2-SO_3H.

While not intending to limit the scope of the invention in any way, Y may also be hydroxymethyl or an ether thereof comprising up to 12 carbon atoms. Thus, compounds having a structure shown below are possible.

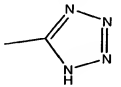


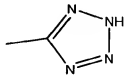
Additionally, ethers of these compounds are also possible. An ether is a functional group wherein a hydrogen of an hydroxyl is replaced by carbon, e.g., Y is CH_2OCH_3, $CH_2OCH_2CH_3$, etc.

Finally, while not intending to limit the scope of the invention in any way, Y may be a tetrazolyl functional group, such as compounds having a structure according to the formula below.

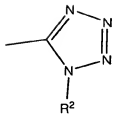


An unsubstituted tetrazolyl functional group has two tautomeric forms, which can rapidly interconvert in aqueous or biological media, and are thus equivalent to one another. These tautomers are shown below.





Additionally, if R^2 is C_1-C_6 alkyl, phenyl, or biphenyl, other isomeric forms of the tetrazolyl functional group such as the one shown below are also possible, unsubstituted and hydrocarbyl substituted tetrazolyl up to C_{12} are considered to be within the scope of the term "tetrazolyl."



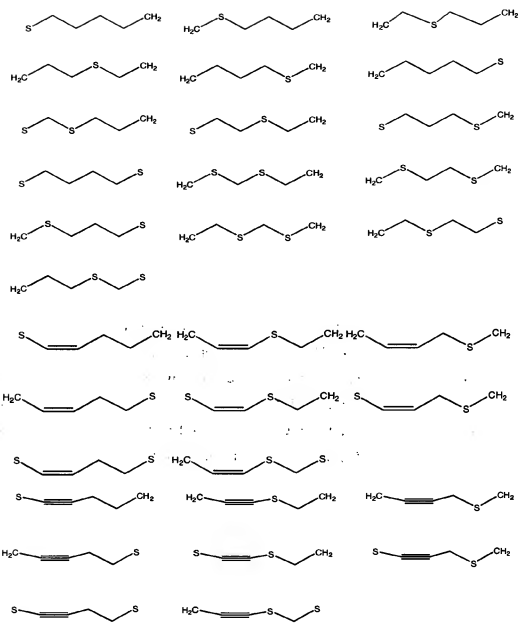
While not intending to limit the scope of the invention in any way, in one embodiment, Y is selected from the group consisting of $CO_2(R^2)$, $CON(R^2)_2$, $CON(OR^2)R^2$, $CON(CH_2CH_2OH)_2$, $CONH(CH_2CH_2OH)$, CH_2OH, $P(O)(OH)_2$, $CONHSO_2R^2$, $SO_2N(R^2)_2$, SO_2NHR^2, and tetrazolyl-R^2; wherein R^2 is independently H, C_1-C_6 alkyl, phenyl, or biphenyl.

In another embodiment Y is not CONH-phenyl or CONH-cyclohexyl.

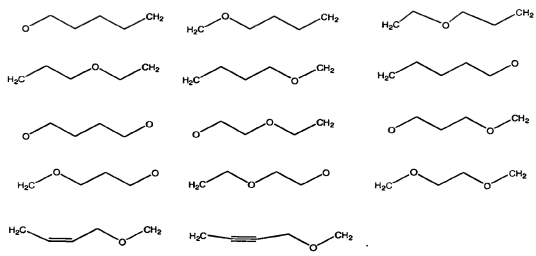
In relation to the identity of A disclosed in the chemical structures presented herein, A is $-(CH_2)_6$-, *cis* $-CH_2CH=CH-(CH_2)_3$-, or $-CH_2C\equiv C-(CH_2)_3$-, wherein 1 or 2 carbon atoms may be substituted with S or O; or A is $-(CH_2)_n$-Ar-$(CH_2)_o$- wherein Ar is interarylene or heterointerarylene, the sum of m and o is from 1 to 4, and wherein one CH_2 may be substituted with S or O.

While not intending to be limiting, A may be $-(CH_2)_6$-, *cis* – $CH_2CH=CH-(CH_2)_3$-, or $-CH_2C\equiv C-(CH_2)_3$-.

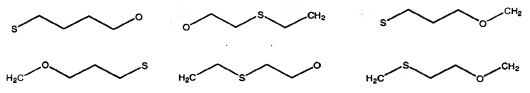
Alternatively, A may be a group which is related to one of these three moieties in that any carbon is substituted with S and/or O. For example, while not intending to limit the scope of the invention in any way, A may be an S substituted moiety such as one of the following or the like.



Alternatively, while not intending to limit the scope of the invention in any way, A may be an O substituted moiety such as one of the following or the like.



Alternatively, while not intending to limit the scope of the invention in any way, A may have both an O and an S substituted into the chain, such as one of the following or the like.



Alternatively, while not intending to limit the scope of the invention in any way, in certain embodiments A is $-(CH_2)_n$-Ar-$(CH_2)_o$- wherein Ar is interarylene or heterointerarylene, the sum of m and o is from 1 to 4, and wherein one CH_2 may be substituted with S or O. In other words, while not intending to limit the scope of the invention in any way,

in one embodiment A comprises from 1 to 4 CH_2 moieties and Ar, e.g. -CH_2-Ar-, -$(CH_2)_2$-Ar-, -CH_2-Ar-CH_2-, -CH_2-Ar-$(CH_2)_2$-, -$(CH_2)_2$-Ar-$(CH_2)_2$-, and the like; or

A comprises O, from 0 to 3 CH_2 moieties, and Ar, e.g., -O-Ar-, Ar-CH_2-O-, -O-Ar-$(CH_2)_2$-, -O-CH_2-Ar-, -O-CH_2-Ar-$(CH_2)_2$, and the like; or

A comprises S, from 0 to 3 CH_2 moieties, and Ar, e.g., -S-Ar-, Ar-CH_2-S-, -S-Ar-$(CH_2)_2$-, -S-CH_2-Ar-, -S-CH_2-Ar-$(CH_2)_2$, -$(CH_2)_2$-S-Ar, and the like.

In another embodiment, the sum of n and o is from 2 to 4 wherein one CH_2 may be substituted with S or O.

In another embodiment, the sum of n and o is 3 wherein one CH_2 may be substituted with S or O.

In another embodiment, the sum of n and o is 2 wherein one CH_2 may be substituted with S or O.

In another embodiment, the sum of n and o is 4 wherein one CH_2 may be substituted with S or O.

Interarylene or heterointerarylene refers to an aryl ring or ring system or a heteroaryl ring or ring system which connects two other parts of a molecule, i.e. the two parts are bonded to the ring in two distinct ring positions. Interarylene or heterointerarylene may be substituted or unsubstituted. Unsubstituted interarylene or heterointerarylene has no substituents other than the two parts of the molecule it connects. Substituted interarylene or heterointerarylene has one or more substitutuents in addition to the two parts of the molecule it connects.

In one embodiment, Ar is substituted or unsubstituted interphenylene, interthienylene, interfurylene, interpyridinylene, interoxazolylene, and interthiazolylene. In another embodiment Ar is interphenylene (Ph). In another embodiment A is $-(CH_2)_2$-Ph-. While not intending to limit scope of the invention in any way, substituents may have 4 or less heavy atoms, or in other words, non hydrogen atoms. Any number of hydrogen atoms required for a particular substituent will also be included. Thus, the substituent may be

hydrocarbyl, i.e. a moiety consisting of only carbon and hydrogen such as alkyl, having up to 4 carbon atoms, including alkyl up to C_4, alkenyl, alkynyl, and the like;

hydrocarbyloxy up to C_3;

CF_3;

halo, such as F, Cl, or Br;

hydroxyl;

NH_2 and alkylamine functional groups up to C_3;

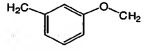
other N or S containing substituents;

and the like.

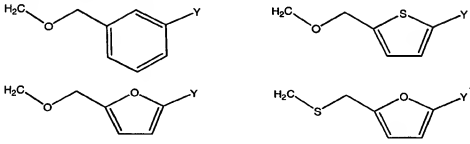
Substituted interarylene or interheteroarylene may have one or more substituents, up to as many as the ring or ring system will bear, and the substituents may be the same or different. Thus, for example, an interarylene ring or interheteroarylene ring may be substituted with chloro and methyl; methyl, OH, and F; CN, NO_2, and ethyl; and the like including any conceivable substituent or combination of substituent possible in light of this disclosure.

In one embodiment A is $-(CH_2)_m$-Ar-$(CH_2)_o$- wherein Ar is interphenylene, the sum of m and o is from 1 to 3, and wherein one CH_2 may be substituted with S or O.

In another embodiment A is -CH_2-Ar-OCH_2-. In another embodiment A is –CH_2-Ar-OCH_2- and Ar is interphenylene. In another embodiment, Ar is 1,3 interaryl or interheteroaryl, where Ar attached at the 1 and 3 positions, such as when A has the structure shown below:



Other examples of 1,3 interaryl or interheteroaryl are exemplified in the following examples of A-Y.

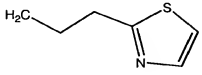
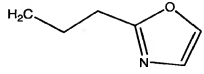
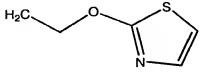
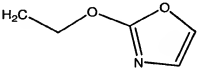
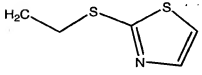
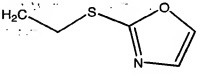


In another embodiment A is $-(CH_2)_6$-, *cis* $-CH_2CH=CH-(CH_2)_3$-, or $-CH_2C\equiv C-(CH_2)_3$-, wherein 1 or 2 carbon atoms may be substituted with S or O; or A is $-(CH_2)_2$-Ph- wherein one CH_2 may be substituted with S or O.

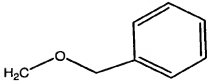
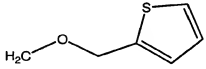
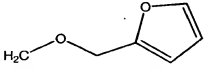
In another embodiment A is $-(CH_2)_6$-, *cis* $-CH_2CH=CH-(CH_2)_3$-, or $-CH_2C\equiv C-(CH_2)_3$-, wherein 1 or 2 carbon atoms may be substituted with S or O; or A is $-(CH_2)_2$-Ph-.

In another embodiment A is not $-(CH_2)_6-$.

In other embodiments, A has one of the following structures, where Y is attached to the oxazolyl or thiazolyl ring.

In other embodiments A is one of the structures shown below, where Y is attached to the phenyl or heteroaryl ring.

In another embodiment A is $-CH_2OCH_2Ar$.

In another embodiment A is $-CH_2SCH_2Ar$.

In another embodiment A is $-(CH_2)_3Ar$.

In another embodiment A is $-CH_2O(CH_2)_4$.

In another embodiment A is $-CH_2S(CH_2)_4$.

In another embodiment A is , $-S(CH_2)_3S(CH_2)_2-$.

In another embodiment A is, $-(CH_2)_4OCH_2-$.

In another embodiment A is, *cis* $-CH_2CH=CH-CH_2OCH_2-$.

In another embodiment A is, $-CH_2CH=CH-CH_2OCH_2-$.

In another embodiment A is, $-(CH_2)_2S(CH_2)_3-$.

In another embodiment A is, $-CH_2-Ph-OCH_2-$, wherein Ph is interphenylene.

In another embodiment A is, $-CH_2-mPh-OCH_2-$, wherein mPh is *m*-interphenylene.

In another embodiment A is, $-CH_2-O-(CH_2)_4-$.

In another embodiment A is, $-CH_2-O-CH_2-Ar-$, wherein Ar is 2,5-interthienylene.

In another embodiment A is, $-CH_2-O-CH_2-Ar-$, wherein Ar is 2,5-interfurylene.

B is aryl or heteroaryl.

Aryl is an unsubstituted or substituted aromatic ring or ring system such as phenyl, naphthyl, biphenyl, and the like.

Heteroaryl is aryl having one or more N, O, or S atoms in the ring, i.e. a ring carbon is substituted by N, O, or S. While not intending to be limiting, examples of heteroaryl include unsubstituted or substituted thienyl, pyridinyl, furyl, benzothienyl, benzofuryl, imidizololyl, indolyl, and the like.

The substituents of aryl or heteroaryl may have up to 12 non-hydrogen atoms each and as many hydrogen atoms as necessary. Thus, while not intending to limit the scope of the invention in any way, the substituents may be:

hydrocarbyl, i.e. a moiety consisting of only carbon and hydrogen such as alkyl, alkenyl, alkynyl, and the like, including linear, branched or cyclic hydrocarbyl, and combinations thereof;

hydrocarbyloxy, meaning O-hydrocarbyl such as OCH_3, OCH_2CH_3, O-cyclohexyl, etc, up to 11 carbon atoms;

other ether substituents such as CH_2OCH_3, $(CH_2)_2OCH(CH_3)_2$, and the like;

thioether substituents including S-hydrocarbyl and other thioether substituents;

hydroxyhydrocarbyl, meaning hydrocarbyl-OH such as CH_2OH, $C(CH_3)_2OH$, etc, up to 11 carbon atoms;

nitrogen substituents such as NO_2, CN, and the like, including

amino, such as NH_2, $NH(CH_2CH_3OH)$, $NHCH_3$, and the like up to 11 carbon atoms;

carbonyl substituents, such as CO_2H, ester, amide, and the like;

halogen, such as chloro, fluoro, bromo, and the like

fluorocarbyl, such as CF_3, CF_2CF_3, etc.;

phosphorous substituents, such as PO_3^{2-}, and the like;

sulfur substituents, including S-hydrocarbyl, SH, SO_3H, SO_2-hydrocarbyl, SO_3-hydrocarbyl, and the like.

In certain embodiments, the number of non-hydrogen atoms is 6 or less in a substituent. In other embodiments, the number of non-hydrogen atoms is 3 or less in a substituent. In other embodiments, the number of non-hydrogen atoms on a substituent is 1.

In certain embodiments, the substituents contain only hydrogen, carbon, oxygen, halogen, nitrogen, and sulfur. In other embodiments, the substituents contain only hydrogen, carbon, oxygen, and halogen.

Unless otherwise indicated, references to aryl, heteroaryl, phenyl, thienyl, benzothienyl, and the like are intended to mean both the substituted and the unsubstituted moiety.

Substituted aryl or heteroaryl may have one or more substituents, up to as many as the ring or ring system will bear, and the substituents may be the same or different. Thus, for example, an aryl ring or a heteroaryl ring may be substituted with chloro and methyl; methyl, OH, and F; CN, NO_2, and ethyl; and the like including any conceivable substituent or combination of substituent possible in light of this disclosure.

Thus, compounds wherein B is any of the above classes or species of aryl or heteroaryl are contemplated herein.

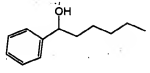
Further, while not intending to limit the scope of the invention in any way, in one embodiment B is phenyl. In another embodiment B is chlorophenyl, meaning phenyl with one or more chloro substituents. In another embodiment D is 3,5-dichlorophenyl. In another embodiment B is

unsubstituted phenyl. In another embodiment B is alkylphenyl. In another embodiment B is t-butylphenyl.

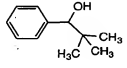
In another embodiment B is not unsubstituted phenyl. In another embodiment B is not chlorophenyl. In another embodiment B is not fluorophenyl. In another embodiment B is not dimethylaminophenyl. In another embodiment B is not unsubstituted phenyl, chlorophenyl, fluorophenyl, or dimethylaminophenyl.

In another embodiment B is hydroxyalkylphenyl, meaning phenyl with a hydroxyalkyl substitutuent such as Ph-$CH(OH)C(CH_3)_3$.

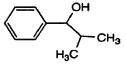
B can also be any of the groups shown below, where the remainder of the molecule attaches to the phenyl ring. The names of these moieties are shown to the right of the structure.



(1-hydroxyhexyl)phenyl

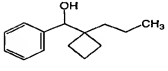


(1-hydroxy-2,2-dimethylpropyl)phenyl

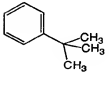


(1-hydroxy-2-methylpropyl)phenyl

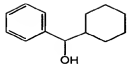
(hydroxymethyl)phenyl



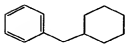
[(1-propylcyclobutyl)hydroxymethyl]phenyl



t-butylphenyl



(cyclohexylhydroxymethyl)phenyl

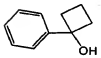


(cyclohexylmethyl)phenyl

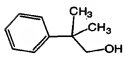
indanyl

indanolyl

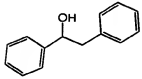
indanonyl



(1-hydroxycyclobutyl)phenyl

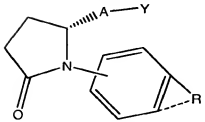


(2-methyl-3-hydroxypropyl)phenyl



(1-hydroxy-2-phenylethyl)phenyl

One compound comprises

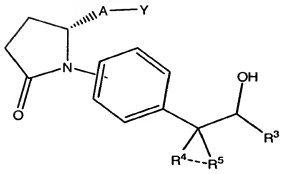


or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof;

wherein a dashed line indicates the presence or absence of a bond

R is hydrocarbyl or hydroxyhydrocarbyl having from 1 to 12 carbon atoms.

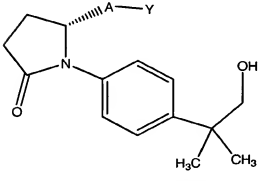
Another embodiment comprises



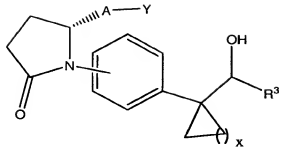
or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof; wherein a dashed line indicates the presence or absence of a bond; R^3, R^4, and R^5 are independently H or C_{1-6} alkyl.

As the dashed line indicates the presence or absence of a bond, R^4 and R^5 may be two separate moieties. For example, while not intending to be limiting, in one embodiment R^4 and R^5 is methyl, and no bond is present where indicated by the dashed line.

For example, a compound according to the formula below

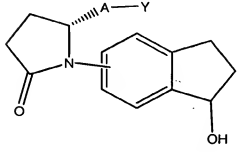


or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof is contemplated. Alternatively, while not intending to limit the scope of the invention in any way, R^4 and R^5 may form a ring. In other words, a compound such as the one shown below is possible, wherein x is from 1 to 6.



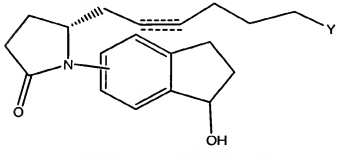
A pharmaceutically acceptable salt, prodrug, or a metabolite thereof is also contemplated.

Another embodiment comprises



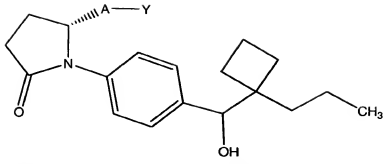
A pharmaceutically acceptable salt, prodrug, or a metabolite thereof is also contemplated.

Other useful compounds comprise



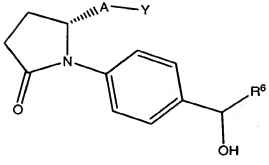
A pharmaceutically acceptable salt, prodrug, or a metabolite thereof is also contemplated.

Other useful examples of compounds comprise



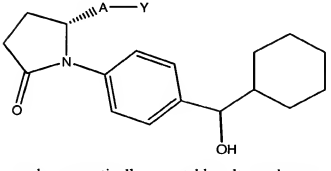
or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof.

Other compounds comprise



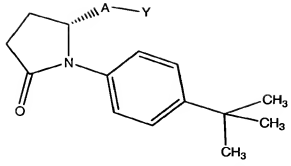
or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof, wherein R^6 is cycloalkyl comprising from 3 to 10 carbon atoms.

Other compounds comprise



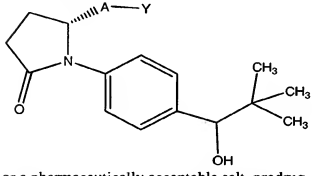
or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof.

Other compounds comprise



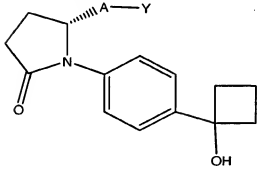
or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof.

Another useful compound is



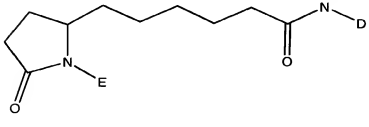
or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof.

Another useful compound is



or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof.

In one embodiment, a compound comprising

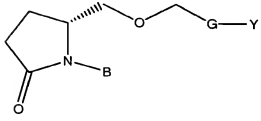


is not used, wherein

D is phenyl or cyclohexyl; and

E is unsubstituted phenyl, chlorophenyl, fluorophenyl, or dimethylaminophenyl.

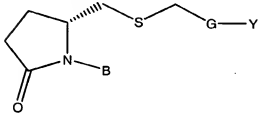
Another compound comprises



or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof;

wherein G is 1,3-interaryl or interheteroaryl, or $-(CH_2)_3-$.

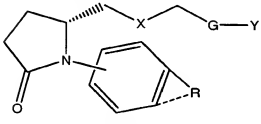
Another compound comprises



or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof;

wherein G is 1,3-interaryl or interheteroaryl, or $-(CH_2)_3-$.

Another compound comprises



or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof;

wherein a dashed line indicates the presence or absence of a bond;

R is hydrocarbyl or hydroxyhydrocarbyl having from 1 to 12 carbon atoms;

X is CH_2, O, or S; and

G is 1,3-interaryl or interheteroaryl, or $-(CH_2)_3-$.

Another compound is an N-aryl or N-heteroaryl gamma lactam which is active at a prostaglandin receptor. This compound may or may not incorporate any other structural limitation disclosed herein.

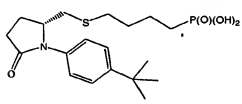
Another compound is an N-aryl or N-heteroaryl gamma lactam which is selectively active at a prostaglandin EP_2 receptor. This compound may or may not incorporate any other structural limitation disclosed herein.

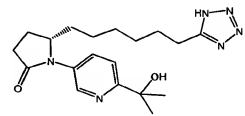
Another compound is an N-aryl or N-heteroaryl gamma lactam which is effective at reducing intraocular pressure in a mammal. This compound may or may not incorporate any other structural limitation disclosed herein.

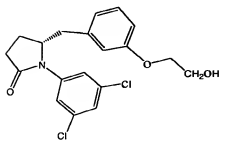
The determination of whether a compound is active at a prostaglandin receptor is well within the ability of a person of ordinary skill in the art. The determination of whether a compound is active at a prostaglandin EP_2 receptor is also well within the ability of a person of ordinary skill in the art. While not intending to limit the scope of the invention in any way, one method of making such determinations is also provided in the examples herein.

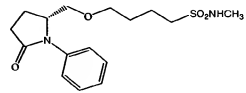
The determination of whether a compound is effective at reducing intraocular pressure in a mammal is well within the ability of a person of ordinary skill in the art. While not intending to limit the scope of the invention in any way, methods of determining whether a compound is effective in reducing intraocular pressure are given for a few exemplary mammals herein.

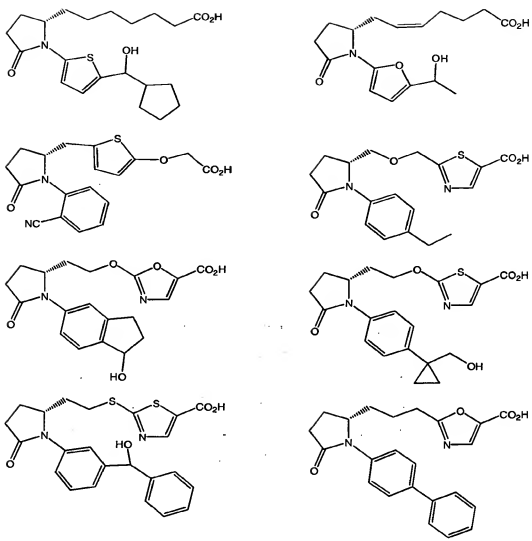
While not intending to limit the scope of the invention in any way, examples of useful compounds are depicted below, and pharmaceutically acceptable salts, prodrugs, or metabolites thereof.











In one embodiment A is $-S(CH_2)_3S(CH_2)_2-$ and B is phenyl.

In another embodiment A is $-(CH_2)_4OCH_2-$ and B is phenyl.

In another embodiment A is *cis* $-CH_2CH=CH-CH_2OCH_2-$ and B is phenyl.

In another embodiment A is $-CH_2CH\equiv CH-CH_2OCH_2-$ and B is phenyl.

In another embodiment A is $-(CH_2)_2S(CH_2)_3-$ and B is phenyl.

In another embodiment A is $-CH_2$-Ph-OCH_2-, wherein Ph is interphenylene, and B is phenyl.

In another embodiment A is $-CH_2$-mPh-OCH_2-, wherein mPh is *m*-interphenylene, and B is phenyl.

In another embodiment A is $-CH_2-O-(CH_2)_4-$ and B is phenyl.

In another embodiment A is $-CH_2-O-CH_2-Ar-$, wherein Ar is 2,5-interthienylene, and B is phenyl.

In another embodiment A is $-CH_2-O-CH_2-Ar-$, wherein Ar is 2,5-interfurylene, and B is phenyl.

As mentioned before, phenyl in the above embodiments means substituted or unsubstituted phenyl unless indicated otherwise.

In one embodiment A is $-S(CH_2)_3S(CH_2)_2-$ and B is (1-hydroxyhexyl)phenyl.

In another embodiment A is $-(CH_2)_4OCH_2-$ and B is (1-hydroxyhexyl)phenyl.

In another embodiment A is *cis* $-CH_2CH=CH-CH_2OCH_2-$ and B is (1-hydroxyhexyl)phenyl.

In another embodiment A is $-CH_2CH\equiv CH-CH_2OCH_2-$ and B is (1-hydroxyhexyl)phenyl.

In another embodiment A is $-(CH_2)_2S(CH_2)_3-$ and B is (1-hydroxyhexyl)phenyl.

In another embodiment A is $-CH_2-Ph-OCH_2-$, wherein Ph is interphenylene, and B is (1-hydroxyhexyl)phenyl.

In another embodiment A is $-CH_2-mPh-OCH_2-$, wherein mPh is *m*-interphenylene, and B is (1-hydroxyhexyl)phenyl.

In another embodiment A is $-CH_2-O-(CH_2)_4-$ and B is (1-hydroxyhexyl)phenyl.

In another embodiment A is $-CH_2-O-CH_2-Ar-$, wherein Ar is 2,5-interthienylene, and B is (1-hydroxyhexyl)phenyl.

In another embodiment A is $-CH_2-O-CH_2-Ar-$, wherein Ar is 2,5-interfurylene, and B is (1-hydroxyhexyl)phenyl.

In another embodiment A is $-S(CH_2)_3S(CH_2)_2-$ and B is (1-hydroxy-2,2-dimethylpropyl)phenyl.

In another embodiment A is $-(CH_2)_4OCH_2-$ and B is (1-hydroxy-2,2-dimethylpropyl)phenyl.

In another embodiment A is *cis* $-CH_2CH=CH-CH_2OCH_2-$ and B is (1-hydroxy-2,2-dimethylpropyl)phenyl.

In another embodiment A is $-CH_2CH\equiv CH-CH_2OCH_2-$ and B is (1-hydroxy-2,2-dimethylpropyl)phenyl.

In another embodiment A is $-(CH_2)_2S(CH_2)_3-$ and B is (1-hydroxy-2,2-dimethylpropyl)phenyl.

In another embodiment A is $-CH_2$-Ph-OCH_2-, wherein Ph is interphenylene, and B is (1-hydroxy-2,2-dimethylpropyl)phenyl.

In another embodiment A is $-CH_2$-mPh-OCH_2-, wherein mPh is *m*-interphenylene, and B is (1-hydroxy-2,2-dimethylpropyl)phenyl.

In another embodiment A is $-CH_2-O-(CH_2)_4-$ and B is (1-hydroxy-2,2-dimethylpropyl)phenyl.

In another embodiment A is $-CH_2-O-CH_2$-Ar-, wherein Ar is 2,5-interthienylene, and B is (1-hydroxy-2,2-dimethylpropyl)phenyl.

In another embodiment A is $-CH_2-O-CH_2$-Ar-, wherein Ar is 2,5-interfurylene, and B is (1-hydroxy-2,2-dimethylpropyl)phenyl.

In another embodiment A is $-S(CH_2)_3S(CH_2)_2-$ and B is (1-hydroxy-2-methylpropyl)phenyl.

In another embodiment A is $-(CH_2)_4OCH_2-$ and B is (1-hydroxy-2-methylpropyl)phenyl.

In another embodiment A is *cis* $-CH_2CH=CH-CH_2OCH_2-$ and B is (1-hydroxy-2-methylpropyl)phenyl.

In another embodiment A is $-CH_2CH\equiv CH-CH_2OCH_2-$ and B is (1-hydroxy-2-methylpropyl)phenyl.

In another embodiment A is $-(CH_2)_2S(CH_2)_3-$ and B is (1-hydroxy-2-methylpropyl)phenyl.

In another embodiment A is $-CH_2$-Ph-OCH_2-, wherein Ph is interphenylene, and B is (1-hydroxy-2-methylpropyl)phenyl.

In another embodiment A is -CH_2-mPh-OCH_2-, wherein mPh is *m*-interphenylene, and B is (1-hydroxy-2-methylpropyl)phenyl.

In another embodiment A is -CH_2-O-$(CH_2)_4$- and B is (1-hydroxy-2-methylpropyl)phenyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interthienylene, and B is (1-hydroxy-2-methylpropyl)phenyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interfurylene, and B is (1-hydroxy-2-methylpropyl)phenyl.

In another embodiment A is -$S(CH_2)_3S(CH_2)_2$- and B is (hydroxymethyl)phenyl.

In another embodiment A is -$(CH_2)_4OCH_2$- and B is (hydroxymethyl)phenyl.

In another embodiment A is *cis* –CH_2CH=CH-CH_2OCH_2- and B is (hydroxymethyl)phenyl.

In another embodiment A is –$CH_2C{\equiv}CH$-CH_2OCH_2- and B is (hydroxymethyl)phenyl.

In another embodiment A is -$(CH_2)_2S(CH_2)_3$- and B is (hydroxymethyl)phenyl.

In another embodiment A is -CH_2-Ph-OCH_2-, wherein Ph is interphenylene, and B is (hydroxymethyl)phenyl.

In another embodiment A is -CH_2-mPh-OCH_2-, wherein mPh is *m*-interphenylene, and B is (hydroxymethyl)phenyl.

In another embodiment A is -CH_2-O-$(CH_2)_4$- and B is (hydroxymethyl)phenyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interthienylene, and B is (hydroxymethyl)phenyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interfurylene, and B is (hydroxymethyl)phenyl.

In another embodiment A is -$S(CH_2)_3S(CH_2)_2$- and B is [(1-propylcyclobutyl)hydroxymethyl]phenyl.

In another embodiment A is $-(CH_2)_4OCH_2-$ and B is [(1-propylcyclobutyl)hydroxymethyl]phenyl.

In another embodiment A is *cis* $-CH_2CH=CH-CH_2OCH_2-$ and B is [(1-propylcyclobutyl)hydroxymethyl]phenyl.

In another embodiment A is $-CH_2CH\equiv CH-CH_2OCH_2-$ and B is [(1-propylcyclobutyl)hydroxymethyl]phenyl.

In another embodiment A is $-(CH_2)_2S(CH_2)_3-$ and B is [(1-propylcyclobutyl)hydroxymethyl]phenyl.

In another embodiment A is $-CH_2$-Ph-OCH_2-, wherein Ph is interphenylene, and B is [(1-propylcyclobutyl)hydroxymethyl]phenyl.

In another embodiment A is $-CH_2$-mPh-OCH_2-, wherein mPh is *m*-interphenylene, and B is [(1-propylcyclobutyl)hydroxymethyl]phenyl.

In another embodiment A is $-CH_2-O-(CH_2)_4-$ and B is [(1-propylcyclobutyl)hydroxymethyl]phenyl.

In another embodiment A is $-CH_2-O-CH_2-Ar-$, wherein Ar is 2,5-interthienylene, and B is [(1-propylcyclobutyl)hydroxymethyl]phenyl.

In another embodiment A is $-CH_2-O-CH_2-Ar-$, wherein Ar is 2,5-interfurylene, and B is [(1-propylcyclobutyl)hydroxymethyl]phenyl.

In another embodiment A is $-S(CH_2)_3S(CH_2)_2-$ and B is t-butylphenyl.

In another embodiment A is $-(CH_2)_4OCH_2-$ and B is t-butylphenyl.

In another embodiment A is *cis* $-CH_2CH=CH-CH_2OCH_2-$ and B is t-butylphenyl.

In another embodiment A is $-CH_2CH\equiv CH-CH_2OCH_2-$ and B is t-butylphenyl.

In another embodiment A is $-(CH_2)_2S(CH_2)_3-$ and B is t-butylphenyl.

In another embodiment A is $-CH_2$-Ph-OCH_2-, wherein Ph is interphenylene, and B is t-butylphenyl.

In another embodiment A is $-CH_2$-mPh-OCH_2-, wherein mPh is *m*-interphenylene, and B is t-butylphenyl.

In another embodiment A is $-CH_2-O-(CH_2)_4-$ and B is t-butylphenyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interthienylene, and B is t-butylphenyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interfurylene, and B is t-butylphenyl.

In another embodiment A is -$S(CH_2)_3S(CH_2)_2$- and B is (cyclohexylhydroxymethyl)phenyl.

In another embodiment A is -$(CH_2)_4OCH_2$- and B is (cyclohexylhydroxymethyl)phenyl.

In another embodiment A is *cis* –CH_2CH=CH-CH_2OCH_2- and B is (cyclohexylhydroxymethyl)phenyl.

In another embodiment A is –CH_2CH≡CH-CH_2OCH_2- and B is (cyclohexylhydroxymethyl)phenyl.

In another embodiment A is -$(CH_2)_2S(CH_2)_3$- and B is (cyclohexylhydroxymethyl)phenyl.

In another embodiment A is -CH_2-Ph-OCH_2-, wherein Ph is interphenylene, and B is (cyclohexylhydroxymethyl)phenyl.

In another embodiment A is -CH_2-mPh-OCH_2-, wherein mPh is *m*-interphenylene, and B is (cyclohexylhydroxymethyl)phenyl.

In another embodiment A is -CH_2-O-$(CH_2)_4$- and B is (cyclohexylhydroxymethyl)phenyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interthienylene, and B is (cyclohexylhydroxymethyl)phenyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interfurylene, and B is (cyclohexylhydroxymethyl)phenyl.

In another embodiment A is -$S(CH_2)_3S(CH_2)_2$- and B is (cyclohexylmethyl)phenyl.

In another embodiment A is -$(CH_2)_4OCH_2$- and B is (cyclohexylmethyl)phenyl.

In another embodiment A is *cis* –CH_2CH=CH-CH_2OCH_2- and B is (cyclohexylmethyl)phenyl.

In another embodiment A is $-CH_2CH{\equiv}CH\text{-}CH_2OCH_2-$ and B is (cyclohexylmethyl)phenyl.

In another embodiment A is $-(CH_2)_2S(CH_2)_3-$ and B is (cyclohexylmethyl)phenyl.

In another embodiment A is $-CH_2\text{-Ph-}OCH_2-$, wherein Ph is interphenylene, and B is (cyclohexylmethyl)phenyl.

In another embodiment A is $-CH_2\text{-mPh-}OCH_2-$, wherein mPh is *m*-interphenylene, and B is (cyclohexylmethyl)phenyl.

In another embodiment A is $-CH_2\text{-O-}(CH_2)_4-$ and B is (cyclohexylmethyl)phenyl.

In another embodiment A is $-CH_2\text{-O-}CH_2\text{-Ar-}$, wherein Ar is 2,5-interthienylene, and B is (cyclohexylmethyl)phenyl.

In another embodiment A is $-CH_2\text{-O-}CH_2\text{-Ar-}$, wherein Ar is 2,5-interfurylene, and B is (cyclohexylmethyl)phenyl.

In another embodiment A is $-S(CH_2)_3S(CH_2)_2-$ and B is indanyl.

In another embodiment A is $-(CH_2)_4OCH_2-$ and B is indanyl.

In another embodiment A is *cis* $-CH_2CH{=}CH\text{-}CH_2OCH_2-$ and B is indanyl.

In another embodiment A is $-CH_2CH{\equiv}CH\text{-}CH_2OCH_2-$ and B is indanyl.

In another embodiment A is $-(CH_2)_2S(CH_2)_3-$ and B is indanyl.

In another embodiment A is $-CH_2\text{-Ph-}OCH_2-$, wherein Ph is interphenylene, and B is indanyl.

In another embodiment A is $-CH_2\text{-mPh-}OCH_2-$, wherein mPh is *m*-interphenylene, and B is indanyl.

In another embodiment A is $-CH_2\text{-O-}(CH_2)_4-$ and B is indanyl.

In another embodiment A is $-CH_2\text{-O-}CH_2\text{-Ar-}$, wherein Ar is 2,5-interthienylene, and B is indanyl.

In another embodiment A is $-CH_2\text{-O-}CH_2\text{-Ar-}$, wherein Ar is 2,5-interfurylene, and B is indanyl.

In another embodiment A is $-S(CH_2)_3S(CH_2)_2-$ and B is indanolyl.

In another embodiment A is -$(CH_2)_4OCH_2$- and B is indanolyl.

In another embodiment A is *cis* –CH_2CH=CH-CH_2OCH_2- and B is indanolyl.

In another embodiment A is –$CH_2CH{\equiv}CH$-CH_2OCH_2- and B is indanolyl.

In another embodiment A is -$(CH_2)_2S(CH_2)_3$- and B is indanolyl.

In another embodiment A is -CH_2-Ph-OCH_2-, wherein Ph is interphenylene, and B is indanolyl.

In another embodiment A is -CH_2-mPh-OCH_2-, wherein mPh is *m*-interphenylene, and B is indanolyl.

In another embodiment A is -CH_2-O-$(CH_2)_4$- and B is indanolyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interthienylene, and B is indanolyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interfurylene, and B is indanolyl.

In another embodiment A is -$S(CH_2)_3S(CH_2)_2$- and B is indanonyl.

In another embodiment A is -$(CH_2)_4OCH_2$- and B is indanonyl.

In another embodiment A is *cis* –CH_2CH=CH-CH_2OCH_2- and B is indanonyl.

In another embodiment A is –$CH_2CH{\equiv}CH$-CH_2OCH_2- and B is indanonyl.

In another embodiment A is -$(CH_2)_2S(CH_2)_3$- and B is indanonyl.

In another embodiment A is -CH_2-Ph-OCH_2-, wherein Ph is interphenylene, and B is indanonyl.

In another embodiment A is -CH_2-mPh-OCH_2-, wherein mPh is *m*-interphenylene, and B is indanonyl.

In another embodiment A is -CH_2-O-$(CH_2)_4$- and B is indanonyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interthienylene, and B is indanonyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interfurylene, and B is indanonyl.

In another embodiment A is -$S(CH_2)_3S(CH_2)_2$- and B is (1-hydroxycyclobutyl)phenyl.

In another embodiment A is -$(CH_2)_4OCH_2$- and B is (1-hydroxycyclobutyl)phenyl.

In another embodiment A is *cis* –CH_2CH=CH-CH_2OCH_2- and B is (1-hydroxycyclobutyl)phenyl.

In another embodiment A is –CH_2CH≡CH-CH_2OCH_2- and B is (1-hydroxycyclobutyl)phenyl.

In another embodiment A is -$(CH_2)_2S(CH_2)_3$- and B is (1-hydroxycyclobutyl)phenyl.

In another embodiment A is -CH_2-Ph-OCH_2-, wherein Ph is interphenylene, and B is (1-hydroxycyclobutyl)phenyl.

In another embodiment A is -CH_2-mPh-OCH_2-, wherein mPh is *m*-interphenylene, and B is (1-hydroxycyclobutyl)phenyl.

In another embodiment A is -CH_2-O-$(CH_2)_4$- and B is (1-hydroxycyclobutyl)phenyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interthienylene, and B is (1-hydroxycyclobutyl)phenyl.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interfurylene, and B is (1-hydroxycyclobutyl)phenyl.

In another embodiment A is -$S(CH_2)_3S(CH_2)_2$- and B is (2-methyl-3-hydroxypropyl)phenyl.

In another embodiment A is -$(CH_2)_4OCH_2$- and B is (2-methyl-3-hydroxypropyl)phenyl.

In another embodiment A is *cis* –CH_2CH=CH-CH_2OCH_2- and B is (2-methyl-3-hydroxypropyl)phenyl.

In another embodiment A is –CH_2CH≡CH-CH_2OCH_2- and B is (2-methyl-3-hydroxypropyl)phenyl.

In another embodiment A is -$(CH_2)_2S(CH_2)_3$- and B is (2-methyl-3-hydroxypropyl)phenyl.

In another embodiment A is $-CH_2-Ph-OCH_2-$, wherein Ph is interphenylene, and B is (2-methyl-3-hydroxypropyl)phenyl.

In another embodiment A is $-CH_2-mPh-OCH_2-$, wherein mPh is *m*-interphenylene, and B is (2-methyl-3-hydroxypropyl)phenyl.

In another embodiment A is $-CH_2-O-(CH_2)_4-$ and B is (2-methyl-3-hydroxypropyl)phenyl.

In another embodiment A is $-CH_2-O-CH_2-Ar-$, wherein Ar is 2,5-interthienylene, and B is (2-methyl-3-hydroxypropyl)phenyl.

In another embodiment A is $-CH_2-O-CH_2-Ar-$, wherein Ar is 2,5-interfurylene, and B is (2-methyl-3-hydroxypropyl)phenyl.

In another embodiment A is $-S(CH_2)_3S(CH_2)_2-$ and B is (1-hydroxy-2-phenylethyl)phenyl.

In another embodiment A is $-(CH_2)_4OCH_2-$ and B is (1-hydroxy-2-phenylethyl)phenyl.

In another embodiment A is *cis* $-CH_2CH=CH-CH_2OCH_2-$ and B is (1-hydroxy-2-phenylethyl)phenyl.

In another embodiment A is $-CH_2CH\equiv CH-CH_2OCH_2-$ and B is (1-hydroxy-2-phenylethyl)phenyl.

In another embodiment A is $-(CH_2)_2S(CH_2)_3-$ and B is (1-hydroxy-2-phenylethyl)phenyl.

In another embodiment A is $-CH_2-Ph-OCH_2-$, wherein Ph is interphenylene, and B is (1-hydroxy-2-phenylethyl)phenyl.

In another embodiment A is $-CH_2-mPh-OCH_2-$, wherein mPh is *m*-interphenylene, and B is (1-hydroxy-2-phenylethyl)phenyl.

In another embodiment A is $-CH_2-O-(CH_2)_4-$ and B is (1-hydroxy-2-phenylethyl)phenyl.

In another embodiment A is $-CH_2-O-CH_2-Ar-$, wherein Ar is 2,5-interthienylene, and B is (1-hydroxy-2-phenylethyl)phenyl.

In another embodiment A is $-CH_2-O-CH_2-Ar-$, wherein Ar is 2,5-interfurylene, and B is (1-hydroxy-2-phenylethyl)phenyl.

Another embodiment comprises a compound selected from the group consisting of

5-[(R)-1-(4-*tert*-Butyl-phenyl)-5-oxo-pyrrolidin-2-ylmethoxy]-pentanoic acid;

3-[(R)-1-(4-*tert*-Butyl-phenyl)-5-oxo-pyrrolidin-2-ylmethoxymethyl]-benzoic acid;

5-[(R)-1-(4-*tert*-Butyl-phenyl)-5-oxo-pyrrolidin-2-ylmethoxymethyl]-furan-2-carboxylic acid;

5-[(R)-1-(4-*tert*-Butyl-phenyl)-5-oxo-pyrrolidin-2-ylmethoxymethyl]-thiophene-2-carboxylic acid;

7-[(S)-1-(4-*tert*-Butyl-phenyl)-5-oxo-pyrrolidin-2-yl]-heptanoic acid;

5-{(R)-1-[4-(1-Hydroxy-hexyl)-phenyl]-5-oxo-pyrrolidin-2-ylmethoxymethyl}-furan-2-carboxylic acid;

5-{(R)-1-[4-(1-Hydroxy-2-methyl-propyl)-phenyl]-5-oxo-pyrrolidin-2-ylmethoxymethyl}-furan-2-carboxylic acid;

5-{(R)-1-[4-(1-Hydroxy-2-phenyl-ethyl)-phenyl]-5-oxo-pyrrolidin-2-ylmethoxymethyl}-furan-2-carboxylic acid; and

5-{(R)-1-[4-(1-Hydroxy-hexyl)-phenyl]-5-oxo-pyrrolidin-2-ylmethoxymethyl}-thiophene-2-carboxylic acid.

The compounds of disclosed herein are useful for the prevention or treatment of glaucoma or ocular hypertension in mammals, or for the manufacture of a medicament for the treatment of glaucoma or ocular hypertension. They are also useful for the treatment of those diseases disclosed in the art as being amenable to treatment by prostaglandin EP_2 agonist, such as the ones listed previously.

A "pharmaceutically acceptable salt" is any salt that retains the activity of the parent compound and does not impart any additional deleterious or untoward effects on the subject to which it is administered and in the context in which it is administered compared to the parent compound. A pharmaceutically acceptable salt also refers to any salt which may form in vivo as a result of administration of an acid, another salt, or a prodrug which is converted into an acid or salt.

Pharmaceutically acceptable salts of acidic functional groups may be derived from organic or inorganic bases. The salt may comprise a mono or polyvalent ion. Of particular interest are the inorganic ions, lithium, sodium, potassium, calcium, and magnesium. Organic salts may be made with amines, particularly ammonium salts such as mono-, di- and trialkyl amines or ethanol amines. Salts may also be formed with caffeine, tromethamine and similar molecules. Hydrochloric acid or some other pharmaceutically acceptable acid may form a salt with a compound that includes a basic group, such as an amine or a pyridine ring.

A "prodrug" is a compound which is converted to a therapeutically active compound after administration, and the term should be interpreted as broadly herein as is generally understood in the art. While not intending to limit the scope of the invention, conversion may occur by hydrolysis of an ester group or some other biologically labile group. Generally, but not necessarily, a prodrug is inactive or less active than the therapeutically active compound to which it is converted. Ester prodrugs of the compounds disclosed herein are specifically contemplated. An ester may be derived from a carboxylic acid of C1 (i.e. the terminal carboxylic acid of a natural prostaglandin), or an ester may be derived from a carboxylic acid functional group on another part of the molecule, such as on a phenyl ring. While not intending to be limiting, an ester may be an alkyl ester, an aryl ester, or a heteroaryl ester. The term alkyl has the meaning generally understood by those skilled in the art and refers to linear, branched, or cyclic alkyl moieties. $C_{1\text{-}6}$ alkyl esters are particularly useful, where alkyl part of the ester has from 1 to 6 carbon atoms and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, pentyl isomers, hexyl isomers, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and combinations thereof having from 1-6 carbon atoms, etc.

A metabolite is broadly defined as a compound which is formed in vivo from the disclosed compound.

Those skilled in the art will readily understand that for administration or the manufacture of medicaments the compounds disclosed herein can be admixed with pharmaceutically acceptable excipients which per se are well

known in the art. Specifically, a drug to be administered systemically, it may be confected as a powder, pill, tablet or the like, or as a solution, emulsion, suspension, aerosol, syrup or elixir suitable for oral or parenteral administration or inhalation.

For solid dosage forms or medicaments, non-toxic solid carriers include, but are not limited to, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, the polyalkylene glycols, talcum, cellulose, glucose, sucrose and magnesium carbonate. The solid dosage forms may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Pat. Nos. 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release. Liquid pharmaceutically administrable dosage forms can, for example, comprise a solution or suspension of one or more of the presently useful compounds and optional pharmaceutical adjutants in a carrier, such as for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like. Typical examples of such auxiliary agents are sodium acetate, sorbitan monolaurate, triethanolamine, sodium acetate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 16th Edition, 1980. The composition of the formulation to be administered, in any event, contains a quantity of one or more of the presently useful compounds in an amount effective to provide the desired therapeutic effect.

Parenteral administration is generally characterized by injection, either subcutaneously, intramuscularly or intravenously. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms

suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol and the like. In addition, if desired, the injectable pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like.

The amount of the presently useful compound or compounds administered is, of course, dependent on the therapeutic effect or effects desired, on the specific mammal being treated, on the severity and nature of the mammal's condition, on the manner of administration, on the potency and pharmacodynamics of the particular compound or compounds employed, and on the judgment of the prescribing physician. The therapeutically effective dosage of the presently useful compound or compounds is preferably in the range of about 0.5 or about 1 to about 100 mg/kg/day.

A liquid which is ophthalmically acceptable is formulated such that it can be administered topically to the eye. The comfort should be maximized as much as possible, although sometimes formulation considerations (e.g. drug stability) may necessitate less than optimal comfort. In the case that comfort cannot be maximized, the liquid should be formulated such that the liquid is tolerable to the patient for topical ophthalmic use. Additionally, an ophthalmically acceptable liquid should either be packaged for single use, or contain a preservative to prevent contamination over multiple uses.

For ophthalmic application, solutions or medicaments are often prepared using a physiological saline solution as a major vehicle. Ophthalmic solutions should preferably be maintained at a comfortable pH with an appropriate buffer system. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

Preservatives that may be used in the pharmaceutical compositions of the present invention include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate. A useful surfactant is, for example, Tween 80. Likewise, various useful vehicles may be used in the ophthalmic preparations of the present invention. These

vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose and purified water.

Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. Accordingly, buffers include acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

In a similar vein, an ophthalmically acceptable antioxidant for use in the present invention includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

Other excipient components which may be included in the ophthalmic preparations are chelating agents. A useful chelating agent is edetate disodium, although other chelating agents may also be used in place or in conjunction with it.

The ingredients are usually used in the following amounts:

Ingredient	Amount (% w/v)
active ingredient	about 0.001-5
preservative	0-0.10
vehicle	0-40
tonicity adjustor	1-10
buffer	0.01-10
pH adjustor	q.s. pH 4.5-7.5
antioxidant	as needed
surfactant	as needed
purified water	as needed to make 100%

For topical use, creams, ointments, gels, solutions or suspensions, etc., containing the compound disclosed herein are employed. Topical formulations

may generally be comprised of a pharmaceutical carrier, cosolvent, emulsifier, penetration enhancer, preservative system, and emollient.

The actual dose of the active compounds of the present invention depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

The compounds disclosed herein are also useful in combination with other drugs useful for the treatment of glaucoma or other conditions.

For the treatment of glaucoma, combination treatment with the following classes of drugs are contemplated:

β-Blockers (or β-adrenergic antagonists) including carteolol, levobunolol, metiparanolol, timolol hemihydrate, timolol maleate, β1-selective antagonists such as betaxolol, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Adrenergic Agonists including

non-selective adrenergic agonists such as epinephrine borate, epinephrine hydrochloride, and dipivefrin, and the like, or pharmaceutically acceptable salts or prodrugs thereof; and

α_2-selective adrenergic agonists such as apraclonidine, brimonidine, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Carbonic Anhydrase Inhibitors including acetazolamide, dichlorphenamide, methazolamide, brinzolamide, dorzolamide, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Cholinergic Agonists including

direct acting cholinergic agonists such as carbachol, pilocarpine hydrochloride, pilocarbine nitrate, pilocarpine, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

chlolinesterase inhibitors such as demecarium, echothiophate, physostigmine, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Glutamate Antagonists and other neuroprotective agents such as Ca^{2+} channel blockers such as memantine, amantadine, rimantadine, nitroglycerin, dextrophan, detromethorphan, CGS-19755, dihydropyridines, verapamil,

emopamil, benzothiazepines, bepridil, diphenylbutylpiperidines, diphenylpiperazines, HOE 166 and related drugs, fluspirilene, eliprodil, ifenprodil, CP-101,606, tibalosine, 2309BT, and 840S, flunarizine, nicardipine, nifedimpine, nimodipine, barnidipine, verapamil, lidoflazine, prenylamine lactate, amiloride, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Prostamides such as bimatoprost, or pharmaceutically acceptable salts or prodrugs thereof; and

Prostaglandins including travoprost, UFO-21, chloprostenol, fluprostenol, 13,14-dihydro-chloprostenol, isopropyl unoprostone, latanoprost and the like.

Cannabinoids including CB1 agonists such as WIN-55212-2 and CP-55940 and the like, or pharmaceutically acceptable salts or prodrugs thereof.

For treatment of diseases affecting the eye including glaucoma, these compounds can be administered topically, periocularly, intraocularly, or by any other effective means known in the art.

Treatment of inflammatory bowel disease may be accomplished by the administration of the compounds described herein to the suffering mammal. Inflammatory bowel disease describes a variety of diseases characterized by inflammation of the bowels including, but not limited to, ulcerative colitis and Crohn's disease. Treatment may be accomplished by oral administration, by suppository, or parenteral administration, or some other suitable method.

While not intending to limit the scope of the invention in any way, delivery of the compounds disclosed herein to the colon via oral dosage forms may be accomplished by any of a number of methods known in the art. For example, reviews by Chourasia and Jain in J Pharm Pharmaceut Sci 6 (1): 33-66, 2003 and Shareef et. al (AAPS PharmSci 2003; 5 (2) Article 17) describe a number of useful methods. While not intending to limit the scope of the invention in any way these methods include 1) administration of a prodrug, including an azo or a carbohydrate based prodrug; 2) coating the drug with, or encapsulating or impregnating the drug into a polymer designed for delivery to

the colon, 3) time released delivery of the drug, 4) use of a bioadhesive system; and the like.

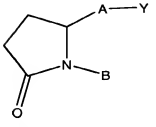
While not intending to be bound in any way by theory, it is believed that intestinal microflora are capable of reductive cleavage of an azo bond leaving the two nitrogen atoms as amine functional groups. While not intending to limit the scope of the invention in any way, the azo prodrug approach has been used to deliver to 5-aminosalicylic acid to the colons of humans in clinical trials for the treatment of inflammatory bowel disease. It is also believed that bacteria of the lower GI also have enzymes which can digest glycosides, glucuronides, cyclodextrins, dextrans, and other carbohydrates, and ester prodrugs formed from these carbohydrates have been shown to deliver the parent active drugs selectively to the colon. For example, in vivo and in vitro studies on rats and guinea pigs with prodrugs of dexamethasone, prednisolone, hydrocortisone, and fludrocortisone, suggest that glycoside conjugates may be useful for the delivery of steroids to the human colon. Other in vivo studies have suggested that glucouronide, cyclodextrin, and dextran prodrugs of steroids or non-steroidal anti-inflammatory drugs are useful for delivery of these drugs to the lower GI tract. An amide of salicylic acid and glutamic acid has been shown to be useful for the delivery of salicylic acid to the colon of rabbit and dog.

While not intending to limit the scope of the invention in any way, carbohydrate polymers such as amylase, arabinogalactan, chitosan, chondroiton sulfate, dextran, guar gum, pectin, xylin, and the like, or azo-group containing polymers can be used to coat a drug compound, or a drug may be impregnated or encapsulated in the polymer. It is believed that after oral administration, the polymers remain stable in the upper GI tract, but are digested by the microflora of the lower GI thus releasing the drug for treatment.

Polymers which are sensitive to pH may also be used since the colon has a higher pH than the upper GI tract. Such polymers are commercially available. For example, Rohm Pharmaceuticals, Darmstadt, Germany, markets pH dependent methacrylate based polymers and copolymers which have varying solubilities over different pH ranges based upon the number of free carboxylate groups in the polymer under the tradename Eudragit®. Several Eudragit®

dosage forms are currently used to deliver salsalazine for the treatment of ulcerative colitis and Crohn's disease. Time release systems, bioadhesive systems, and other delivery systems have also been studied.

One embodiment is use of a compound in the manufacture of a medicament for the treatment of inflammatory bowel disease, said compound comprising



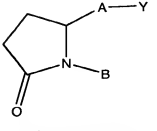
or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof; wherein

Y is an organic acid functional group, or an amide or ester thereof comprising up to 12 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 12 carbon atoms; or Y is a tetrazolyl functional group;

A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be substituted with S or O; or A is $-(CH_2)_m-Ar-(CH_2)_o-$ wherein Ar is interarylene or heterointerarylene, the sum of m and o is from 1 to 4, and wherein one CH_2 may be substituted with S or O; and

B is aryl or heteroaryl.

Another embodiment is use of a compound in the manufacture of a medicament for the treatment of inflammatory bowel disease, said compound comprising



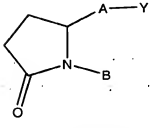
or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof; wherein

Y is an organic acid functional group, or an amide or ester thereof comprising up to 12 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 12 carbon atoms; or Y is a tetrazolyl functional group;

A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be substituted with S or O; or A is $-(CH_2)_m-Ar-(CH_2)_o-$ wherein Ar is interarylene or heterointerarylene, the sum of m and o is from 1 to 4, and wherein one CH_2 may be substituted with S or O; and

B is phenyl.

Another embodiment is use of a compound in the manufacture of a medicament for the treatment of inflammatory bowel disease, said compound comprising



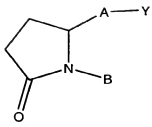
or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof; wherein

Y is an organic acid functional group, or an amide or ester thereof comprising up to 12 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 12 carbon atoms; or Y is a tetrazolyl functional group;

A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be substituted with S or O; or A is $-(CH_2)_m-Ar-(CH_2)_o-$ wherein Ar is interarylene or heterointerarylene, the sum of m and o is from 1 to 4, and wherein one CH_2 may be substituted with S or O; and

B is alkylphenyl.

Another embodiment is use of a compound in the manufacture of a medicament for the treatment of inflammatory bowel disease, said compound comprising



or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof; wherein

Y is an organic acid functional group, or an amide or ester thereof comprising up to 12 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 12 carbon atoms; or Y is a tetrazolyl functional group;

A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be substituted with S or O; or A is $-(CH_2)_m$-Ar-$(CH_2)_o-$ wherein Ar is interarylene or heterointerarylene, the sum of m and o is from 1 to 4, and wherein one CH_2 may be substituted with S or O; and

B is *p-t*-butylphenyl.

Another embodiment is use of a compound in the manufacture of a medicament for the treatment of inflammatory bowel disease, said compound of claim selected from the group consisting of

5-[(R)-1-(4-*tert*-Butyl-phenyl)-5-oxo-pyrrolidin-2-ylmethoxy]-pentanoic acid;

3-[(R)-1-(4-*tert*-Butyl-phenyl)-5-oxo-pyrrolidin-2-ylmethoxymethyl]-benzoic acid;

5-[(R)-1-(4-*tert*-Butyl-phenyl)-5-oxo-pyrrolidin-2-ylmethoxymethyl]-furan-2-carboxylic acid;

5-[(R)-1-(4-*tert*-Butyl-phenyl)-5-oxo-pyrrolidin-2-ylmethoxymethyl]-thiophene-2-carboxylic acid;

7-[(S)-1-(4-*tert*-Butyl-phenyl)-5-oxo-pyrrolidin-2-yl]-heptanoic acid;

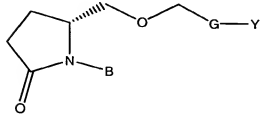
5-{(R)-1-[4-(1-Hydroxy-hexyl)-phenyl]-5-oxo-pyrrolidin-2-ylmethoxymethyl}-furan-2-carboxylic acid;

5-{(R)-1-[4-(1-Hydroxy-2-methyl-propyl)-phenyl]-5-oxo-pyrrolidin-2-ylmethoxymethyl}-furan-2-carboxylic acid;

5-{(R)-1-[4-(1-Hydroxy-2-phenyl-ethyl)-phenyl]-5-oxo-pyrrolidin-2-ylmethoxymethyl}-furan-2-carboxylic acid; and

5-{(R)-1-[4-(1-Hydroxy-hexyl)-phenyl]-5-oxo-pyrrolidin-2-ylmethoxymethyl}-thiophene-2-carboxylic acid.

Another embodiment is use of a compound in the manufacture of a medicament for the treatment of inflammatory bowel disease, said compound of comprising



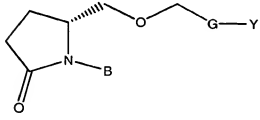
or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof; wherein

Y is an organic acid functional group, or an amide or ester thereof comprising up to 12 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 12 carbon atoms; or Y is a tetrazolyl functional group;

G is 1,3-interaryl or interheteroaryl, or $-(CH_2)_3-$; and

B is aryl or heteroaryl.

Another embodiment is use of a compound in the manufacture of a medicament for the treatment of inflammatory bowel disease, said compound of comprising



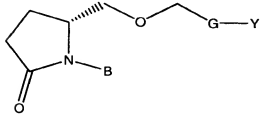
or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof; wherein

Y is an organic acid functional group, or an amide or ester thereof comprising up to 12 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 12 carbon atoms; or Y is a tetrazolyl functional group;

G is 1,3-interaryl or interheteroaryl, or $-(CH_2)_3-$; and

B is phenyl.

Another embodiment is use of a compound in the manufacture of a medicament for the treatment of inflammatory bowel disease, said compound of comprising



or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof;

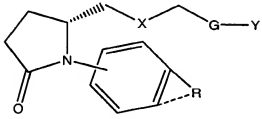
wherein

Y is an organic acid functional group, or an amide or ester thereof comprising up to 12 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 12 carbon atoms; or Y is a tetrazolyl functional group;

G is 1,3-interaryl or interheteroaryl, or $-(CH_2)_3-$; and

B is hydroxyalkylphenyl.

Another embodiment is use of a compound in the manufacture of a medicament for the treatment of inflammatory bowel disease, said compound comprising



or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof;

wherein a dashed line indicates the presence or absence of a bond;

Y is an organic acid functional group, or an amide or ester thereof comprising up to 12 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 12 carbon atoms; or Y is a tetrazolyl functional group;

R is hydrocarbyl or hydroxyhydrocarbyl having from 1 to 12 carbon atoms;

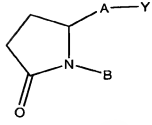
X is CH_2, O, or S; and

G is 1,3-interaryl or interheteroaryl, or $-(CH_2)_3-$.

Another embodiment is use of a compound in the manufacture of a medicament for the treatment of inflammatory bowel disease, said compound

comprising an N-aryl or N-heteroaryl gamma lactam which is effective at reducing intraocular pressure in a mammal.

One embodiment is a compound comprising



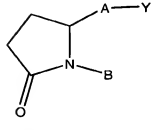
or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof; wherein

Y is an organic acid functional group, or an amide or ester thereof comprising up to 12 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 12 carbon atoms; or Y is a tetrazolyl functional group;

A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be substituted with S or O; or A is $-(CH_2)_m-Ar-(CH_2)_o-$ wherein Ar is interarylene or heterointerarylene, the sum of m and o is from 1 to 4, and wherein one CH_2 may be substituted with S or O; and

B is aryl or heteroaryl.

Another embodiment is a compound comprising



or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof; wherein

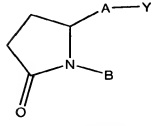
Y is an organic acid functional group, or an amide or ester thereof comprising up to 12 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 12 carbon atoms; or Y is a tetrazolyl functional group;

A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be substituted with S or O; or A is $-(CH_2)_m-Ar-(CH_2)_o-$

wherein Ar is interarylene or heterointerarylene, the sum of m and o is from 1 to 4, and wherein one CH_2 may be substituted with S or O; and

B is phenyl.

Another embodiment is a compound comprising



or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof;

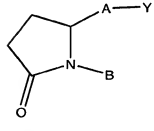
wherein

Y is an organic acid functional group, or an amide or ester thereof comprising up to 12 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 12 carbon atoms; or Y is a tetrazolyl functional group;

A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be substituted with S or O; or A is $-(CH_2)_m-Ar-(CH_2)_o-$ wherein Ar is interarylene or heterointerarylene, the sum of m and o is from 1 to 4, and wherein one CH_2 may be substituted with S or O; and

B is alkylphenyl.

Another embodiment is a compound comprising



or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof;

wherein

Y is an organic acid functional group, or an amide or ester thereof comprising up to 12 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 12 carbon atoms; or Y is a tetrazolyl functional group;

A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be substituted with S or O; or A is $-(CH_2)_m-Ar-(CH_2)_o-$

wherein Ar is interarylene or heterointerarylene, the sum of m and o is from 1 to 4, and wherein one CH_2 may be substituted with S or O; and

B is *p*-*t*-butylphenyl.

Another embodiment is a compound of claim selected from the group consisting of

5-[(R)-1-(4-*tert*-Butyl-phenyl)-5-oxo-pyrrolidin-2-ylmethoxy]-pentanoic acid;

3-[(R)-1-(4-*tert*-Butyl-phenyl)-5-oxo-pyrrolidin-2-ylmethoxymethyl]-benzoic acid;

5-[(R)-1-(4-*tert*-Butyl-phenyl)-5-oxo-pyrrolidin-2-ylmethoxymethyl]-furan-2-carboxylic acid;

5-[(R)-1-(4-*tert*-Butyl-phenyl)-5-oxo-pyrrolidin-2-ylmethoxymethyl]-thiophene-2-carboxylic acid;

7-[(S)-1-(4-*tert*-Butyl-phenyl)-5-oxo-pyrrolidin-2-yl]-heptanoic acid;

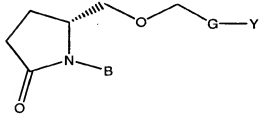
5-{(R)-1-[4-(1-Hydroxy-hexyl)-phenyl]-5-oxo-pyrrolidin-2-ylmethoxymethyl}-furan-2-carboxylic acid;

5-{(R)-1-[4-(1-Hydroxy-2-methyl-propyl)-phenyl]-5-oxo-pyrrolidin-2-ylmethoxymethyl}-furan-2-carboxylic acid;

5-{(R)-1-[4-(1-Hydroxy-2-phenyl-ethyl)-phenyl]-5-oxo-pyrrolidin-2-ylmethoxymethyl}-furan-2-carboxylic acid; and

5-{(R)-1-[4-(1-Hydroxy-hexyl)-phenyl]-5-oxo-pyrrolidin-2-ylmethoxymethyl}-thiophene-2-carboxylic acid.

Another embodiment is a compound of comprising



or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof;

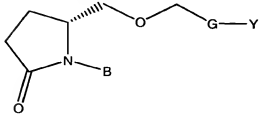
wherein

Y is an organic acid functional group, or an amide or ester thereof comprising up to 12 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 12 carbon atoms; or Y is a tetrazolyl functional group;

G is 1,3-interaryl or interheteroaryl, or $-(CH_2)_3-$; and

B is aryl or heteroaryl.

Another embodiment is a compound of comprising



or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof;

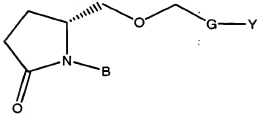
wherein

Y is an organic acid functional group, or an amide or ester thereof comprising up to 12 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 12 carbon atoms; or Y is a tetrazolyl functional group;

G is 1,3-interaryl or interheteroaryl, or $-(CH_2)_3-$; and

B is phenyl.

Another embodiment is a compound of comprising



or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof;

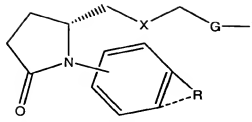
wherein

Y is an organic acid functional group, or an amide or ester thereof comprising up to 12 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 12 carbon atoms; or Y is a tetrazolyl functional group;

G is 1,3-interaryl or interheteroaryl, or $-(CH_2)_3-$; and

B is hydroxyalkylphenyl.

Another embodiment is a compound comprising



or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof;

wherein a dashed line indicates the presence or absence of a bond;

Y is an organic acid functional group, or an amide or ester thereof comprising up to 12 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 12 carbon atoms; or Y is a tetrazolyl functional group;

R is hydrocarbyl or hydroxyhydrocarbyl having from 1 to 12 carbon atoms;

X is CH_2, O, or S; and

G is 1,3-interaryl or interheteroaryl, or $-(CH_2)_3-$.

Another embodiment is a compound comprising an N-aryl or N-heteroaryl gamma lactam which is effective at reducing intraocular pressure in a mammal.

Embodiments contemplated for each compound disclosed herein are use of the compound in the manufacture of a medicament for the treatment of glaucoma or ocular hypertension.

Embodiments contemplated for each compound disclosed herein are use of the compound in the manufacture of a medicament for the treatment of inflammatory bowel disease.

Embodiments contemplated for each compound disclosed herein are methods comprising administering an effective amount of the compound to a mammal for the treatment of glaucoma or ocular hypertension.

Embodiments contemplated for each compound disclosed herein are methods comprising administering an effective amount of the compound to a mammal for the treatment of inflammatory bowel disease.

Embodiments contemplated for each compound disclosed herein are compositions comprising the compound, wherein said compositions are ophthalmically acceptable liquids.

Example 1

5-[(R)-1-(4-*tert*-Butyl-phenyl)-5-oxo-pyrrolidin-2-ylmethoxy]-pentanoic acid **(4)**

Step 1. Arylation of **1** to give **2**

A solution of amide **1** (3.30 g, 14.4 mmol) in 1,4-dioxane (25 mL) was added to a mixture of 4,5-bis(triphenylphosphino)-9,9-dimethylxanthene (xantphos, 600 mg, 1.04 mmol), $Pd_2(dba)_3$ (317 mg, 0.35 mmol) and Cs_2CO_3 (6.46 g, 19.8 mmol). 1-Bromo-4-*tert*-butylbenzene (2.40 mL, 13.8 mmol) was added and the reaction mixture was purged with nitrogen. The mixture was heated at reflux for 19 h, then cooled to room temperature. The reaction mixture was then filtered through celite, washing with CH_2Cl_2, and the filtrate was concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (10% → 20% EtOAc/Hexane, gradient) afforded 3.53 g (71%) of the desired product **2**.

Step 2. Deprotection of **2** to give **3**

HF-pyridine (5 mL) was added to a solution of silyl ether **2** (3.53 g, 9.76 mmol) in MeCN (20 mL) in a plastic bottle. The reaction was stirred at room temperature for 5 h, then was quenched with saturated aqueous $NaHCO_3$ (250 mL). The mixture was extracted with EtOAc (3 x 100 mL). The combined extracts were washed with brine (150 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo to yield 2.14 g (89%) of the desired product **3**.

Step 3. Alkylation of **3** to give the ester of **4**

Sodium hydride (11 mg, 0.46 mmol) was added to a solution of alcohol **3** (100 mg, 0.40 mmol) in THF (3 mL) at 0 °C under nitrogen. After 1 h at 0 °C, methyl 5-bromovalerate (67 μL, 0.47 mmol) was added and the reaction was allowed to warm to room temperature. After 3 h, TLC analysis showed mostly starting alcohol remaining and another portion of bromide (67 μL, 0.47 mmol) was added. After 22 h total reaction time, the reaction was quenched with 1 N HCl and extracted with EtOAc (3 x 25 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (40% EtOAc/Hexane → EtOAc, gradient) afforded 19 mg (13%) of the desired ester.

Step 4. Saponification to give **4**

Aqueous lithium hydroxide (1 N, 0.5 mL) was added to a solution of ester from step 3 above (12.3 mg, 0.034 mmol) in THF (0.7 mL). After 2.5 h at room temperature, the reaction was acidified with 0.25 M HCl (5 mL) then extracted with CH_2Cl_2 (3 x 7 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo to afford 10.2 mg (86%) of the title compound (**4**).

Example 2

3-[(R)-1-(4-tert-Butyl-phenyl)-5-oxo-pyrrolidin-2-ylmethoxymethyl]-benzoic acid (**5**)

Step 1. Alkylation of **3** to give the ester of **5**

Potassium hydride (23.4 mg, 0.58 mmol) and 18-crown-6 (167 mg, 0.63 mmol) were added sequentially to a solution of alcohol **3** (130 mg, 0.53 mmol) in THF (3 mL) at 0 °C. After 1 h at 0 °C, a solution of methyl 3-(chloromethyl)benzoate (prepared from the corresponding acid chloride, pyridine and methanol: see *J. Org. Chem.* **1988**, *53*, 2548-2552; 116 mg, 0.63 mmol) in THF (1.5 mL) was added via cannula and the reaction was allowed to warm to room temperature. After 22.5 h, the reaction was quenched with 0.1 N HCl (10 mL) and extracted with EtOAc (3 x 15 mL). Combined extracts were washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (30% $\rightarrow$ 50% EtOAc/Hexane, gradient) afforded 66 mg (32%) of the desired ester.

Step 2. Saponification to give **5**

Aqueous lithium hydroxide (1 N, 0.4 mL) was added to a solution of ester from step 1 above (33.5 mg, 0.085 mmol) in THF (0.75 mL). After 3.5 h at room temperature, the reaction was acidified with 0.25 M HCl (5 mL) then extracted with CH_2Cl_2 (3 x 10 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (2% MeOH/CH_2Cl_2), followed by preparative thin

layer chromatography (10% MeOH/CH_2Cl_2) afforded 6.6 mg (20%) of the title compound (**5**).

Example 3

5-[(R)-1-(4-tert-Butyl-phenyl)-5-oxo-pyrrolidin-2-ylmethoxymethyl]-furan-2-carboxylic acid (**6**)

Step 1. Alkylation of **3** to give the ester of **6**

Potassium hydride (27 mg, 0.67 mmol) and 18-crown-6 (193 mg, 0.73 mmol) were added sequentially to a solution of alcohol **3** (150 mg, 0.61 mmol) in THF (4 mL) at 0 °C. After 1 h at 0 °C, a solution of ethyl 5-chloromethylfuran-2-carboxylate (commercially available from Aldrich Chemical Company, 138 mg, 0.73 mmol) in THF (1 mL) was added via cannula and the reaction was allowed to warm to room temperature. After 18.5 h, the reaction was quenched with 0.25 N HCl (10 mL) and extracted with EtOAc (3 x 15 mL). Combined extracts were washed with brine (20 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (20% → 50% EtOAc/Hexane, gradient) afforded 78 mg (32%) of the desired ester.

Step 2. Saponification to give **6**

Aqueous lithium hydroxide (1 N, 0.5 mL) was added to a solution of ester from step 1 above (66.7 mg, 0.17 mmol) in THF (0.5 mL). After 3 h at room temperature, the reaction was acidified with 1 N HCl (2 mL) then extracted with CH_2Cl_2 (3 x 10 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo to afford 54.4 mg (88%) of the title compound (**6**).

Example 4

5-[(R)-1-(4-tert-Butyl-phenyl)-5-oxo-pyrrolidin-2-ylmethoxymethyl]-thiophene-2-carboxylic acid (**7**)

Step 1. Alkylation of **3** to give the ester of **7**

Potassium hydride (25.2 mg, 0.63 mmol) and 18-crown-6 (181 mg, 0.68 mmol) were added sequentially to a solution of alcohol **3** (140 mg, 0.57 mmol)

in THF (4 mL) at 0 °C. After 1.5 h at 0 °C, a solution of methyl 5-chloromethylthiophene-2-carboxylate (prepared according to the procedures described in WO2004/037808; 130 mg, 0.68 mmol) in THF (1.5 mL) was added via cannula and the reaction was allowed to warm to room temperature. After 20 h, the reaction was quenched with 0.25 N HCl (15 mL) and extracted with EtOAc (3 x 20 mL). Combined extracts were washed with brine (30 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (20% → 50% EtOAc/Hexane, gradient) afforded 40.7 mg (18%) of the desired ester.

Step 2. Saponification to give **7**

Aqueous lithium hydroxide (1 N, 0.4 mL) was added to a solution of ester from step 1 above (37 mg, 0.092 mmol) in THF (0.75 mL). After 18 h at room temperature, the reaction was acidified with 1 N HCl (7 mL) then extracted with CH_2Cl_2 (3 x 10 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo to afford 22.3 mg (62%) of the title compound (**7**).

Example 5

7-[(S)-1-(4-tert-Butyl-phenyl)-5-oxo-pyrrolidin-2-yl]-heptanoic acid (**10**)

Step 1. Oxidation of **3** to give aldehyde **8**

Molecular sieves (4Å, 300 mg), 4-methylmorpholine *N*-oxide (427 mg, 3.64 mmol) and tetrapropylammonium perruthenate (250 mg, 0.71 mmol) were added sequentially to a solution of alcohol **3** (600 mg, 2.43 mmol) in CH_2Cl_2 (15 mL) at room temperature. After 23 h, the reaction mixture was filtered through celite, washing with CH_2Cl_2 (10 mL). The filtrate was concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (CH_2Cl_2 → 10% EtOAc/CH_2Cl_2, gradient) afforded 92 mg (15%) of the desired aldehyde **8**.

Step 2. Wittig reaction of **8** to give **9**

Potassium bis(trimethylsilyl)amide (0.5 M in PhMe, 1.92 mL, 0.96 mmol) was added to a solution of aldehyde **8** (86 mg, 0.35 mmol) in THF (2 mL) at room temperature. After 15 min at room temperature, the reaction

mixture was cooled to – 55 °C for 10 min before a solution of 5-carboxypentyltriphenylphosphonium bromide (207 mg, 0.45 mmol) was added via cannula. After 10 min at – 55 °C, the reaction was allowed to warm to room temperature. After 18 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl (15 mL) and extracted with EtOAc (3 x 15 mL). Combined extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by preparative thin layer chromatography (5% MeOH/CH_2Cl_2) afforded 10.5 mg (9%) of desired alkene **9**.

Step 3. Hydrogenation of **9** to give **10**

Palladium on carbon (10 wt. %, 2 mg) was added to a solution of alkene **9** (5.8 mg, 0.017 mmol) in MeOH (1 mL). A hydrogen atmosphere was established by evacuating and refilling with hydrogen (3x) and the reaction mixture was stirred under a balloon of hydrogen for 18 h. The reaction mixture was filtered through celite, washing with MeOH, and the filtrate was concentrated in vacuo to afford 4.1 mg (70%) of the title compound (**10**).

Example 6

5-{(R)-1-[4-(1-Hydroxy-hexyl)-phenyl]-5-oxo-pyrrolidin-2-ylmethoxymethyl}-furan-2-carboxylic acid (**17**)

Step 1. Arylation of **1** to give **12**

A solution of amide **1** (2.89 g, 12.60 mmol) in 1,4-dioxane (20 mL) followed by a solution of 1-(4-methoxybenzyloxymethyl)-4-bromobenzene (**11** prepared according to the procedure in U.S. Patent Application Serial No. 09298, filed December 10, 2004, incorporated by reference herein; 3.88 g, 12.63 mmol) were added sequentially to a mixture of xantphos (877 mg, 1.52 mmol), $Pd_2(dba)_3$ (463 mg, 0.51 mmol) and Cs_2CO_3 (3.2 g, 9.82 mmol) via cannula. The reaction mixture was purged with nitrogen and then heated at reflux for 22 h. The reaction mixture was allowed to cool to room temperature then filtered through celite, washing with CH_2Cl_2, and the filtrate was concentrated in vacuo. Purification of the residue by flash column

chromatography on silica gel (5% → 25% EtOAc/Hexane, gradient) afforded 1.70 g (30%) of desired product **12**.

Step 2. Deprotection of **12** to give **13**

HF-pyridine (5 mL) was added to a solution of silyl ether **12** (1.38 g, 3.03 mmol) in MeCN (15 mL) in a plastic bottle at 0 °C. The reaction was stirred at 0 °C for 3 h, then was quenched with saturated aqueous $NaHCO_3$ (250 mL). The mixture was extracted with EtOAc (3 x 100 mL). The combined extracts were washed with brine (100 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (1% → 3% MeOH/CH_2Cl_2, gradient) afforded 464 mg (45%) of desired alcohol **13**.

Step 3. Alkylation of alcohol **13** to give **14**

Potassium hydride (44 mg, 1.10 mmol) and 18-crown-6 (365 mg, 1.38 mmol) were added sequentially to a solution of alcohol **13** (315 mg, 0.92 mmol) in THF (4 mL) at 0 °C. After 1 h at 0 °C, ethyl 5-chloromethylfuran-2-carboxylate (0.28 mL, 1.82 mmol) was added and the reaction was allowed to warm to room temperature. After 22 h, the reaction was quenched with 0.5 N HCl (20 mL) and extracted with EtOAc (3 x 25 mL). Combined extracts were washed with brine (50 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (20% EtOAc/Hexane → EtOAc, gradient) afforded 148 mg (32%) of desired product **14**.

Step 4. Oxidative deprotection of **14** to give **15** and **16**

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 82 mg, 0.36 mmol) was added to a mixture of **14** (143 mg, 0.29 mmol) in CH_2Cl_2 (4 mL) and water (0.2 mL). After 3 h, TLC indicated that starting material remained and another portion of DDQ (82 mg, 0.36 mmol) was added. After a further 1.25 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined extracts were washed with brine (20 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (CH_2Cl_2 → 3% MeOH/CH_2Cl_2, gradient) afforded 38 mg (35%) of the desired

alcohol **15** and 61 mg of impure aldehyde **16**. Aldehyde **16** was further purified by preparative thin layer chromatography (5% MeOH/CH_2Cl_2) to afford 48.7 mg (45%) of aldehyde **16**.

Step 5. Oxidation of **15** to give **16**

Molecular sieves (4Å, 3 mg), 4-methylmorpholine *N*-oxide (12.6 mg, 0.11 mmol) and tetrapropylammonium perruthenate (2.5 mg, 0.007 mmol) were added sequentially to a solution of alcohol **15** (26.8 mg, 0.072 mmol) in CH_2Cl_2 (1.5 mL) at room temperature. After 20 min, the reaction mixture was filtered through celite, washing with CH_2Cl_2 (5 mL). The filtrate was concentrated in vacuo. Purification of the residue by preparative thin layer chromatography (5% MeOH/CH_2Cl_2) afforded 9.6 mg (36%) of the desired aldehyde **16**.

Step 6. Grignard reaction with **16** to give the ester of **17**

Pentyl magnesium bromide (2.0 M in Et_2O, 32 μL, 0.064 mmol) was added to a solution of aldehyde **16** (21.7 mg, 0.058 mmol) in THF (0.4 mL) at – 40 °C under nitrogen. After 25 min, the reaction was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3 x 7 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by preparative thin layer chromatography (5% MeOH/CH_2Cl_2) afforded 10.6 mg (41%) of the desired ester.

Step 7. Saponification to give **17**

Aqueous lithium hydroxide (1 N, 0.1 mL) was added to a solution of ester from step 6 above (8.8 mg, 0.02 mmol) in THF (0.2 mL). After 1 h at room temperature, the reaction was acidified with 0.5 N HCl (1 mL) then extracted with CH_2Cl_2 (3 x 7 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo to afford 8.2 mg (99%) of the title compound (**17**).

Example 7

5-{(R)-1-[4-(1-Hydroxy-2-methyl-propyl)-phenyl]-5-oxo-pyrrolidin-2-ylmethoxymethyl}-furan-2-carboxylic acid (**18**)

Step 1. Grignard reaction with **16** to give the ester of **18**

Isopropyl magnesium chloride (2.0 M in THF, 31 μL, 0.062 mmol) was added to a solution of aldehyde **16** (20.5 mg, 0.055 mmol) in THF (0.4 mL) at – 40 °C under nitrogen. After 35 min, the reaction was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3 x 7 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by preparative thin layer chromatography (5% MeOH/CH_2Cl_2) afforded 5 mg (22%) of the desired ester.

Step 2. Saponification to give **18**

Aqueous lithium hydroxide (1 N, 0.05 mL) was added to a solution of the ester from step 1 above (3.1 mg, 0.007 mmol) in THF (0.15 mL). After 1 h at room temperature, the reaction was acidified with 0.2 N HCl (1 mL) then extracted with CH_2Cl_2 (3 x 7 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo to afford 2.5 mg (86%) of the title compound (**18**).

Example 8

5-{(R)-1-[4-(1-Hydroxy-2-phenyl-ethyl)-phenyl]-5-oxo-pyrrolidin-2-ylmethoxymethyl}-furan-2-carboxylic acid (**19**)

Step 1. Grignard reaction with **16** to give the ester of **19**

Benzyl magnesium chloride (2.0 M in THF, 14 μL, 0.028 mmol) was added to a solution of aldehyde **16** (9.6 mg, 0.026 mmol) in THF (0.3 mL) at – 40 °C under nitrogen. After 45 min, the reaction was warmed to 0 °C. After 25 min at 0 °C, the reaction was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3 x 7 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by preparative thin layer chromatography (7% MeOH/CH_2Cl_2) afforded 3.3 mg (28%) of the desired ester.

Step 2. Saponification to give **19**

Aqueous lithium hydroxide (1 N, 0.05 mL) was added to a solution of the ester from step 1 above (2.4 mg, 0.005 mmol) in THF (0.15 mL). After 2.5 h at room temperature, the reaction was acidified with 0.2 N HCl (1 mL) then extracted with CH_2Cl_2 (3 x 7 mL). Combined extracts were dried (Na_2SO_4),

filtered and concentrated in vacuo to afford 2.2 mg (98%) of the title compound (**19**)

Example 9

5-{(R)-1-[4-(1-Hydroxy-hexyl)-phenyl]-5-oxo-pyrrolidin-2-ylmethoxymethyl}-thiophene-2-carboxylic acid (**23**)

Step 1. Alkylation of **13** to give **20**

Potassium hydride (55.5 mg, 1.38 mmol) and 18-crown-6 (456 mg, 1.73 mmol) were added sequentially to a solution of alcohol **13** (394 mg, 1.15 mmol) in THF (5 mL) at 0 °C. After 1 h at 0 °C, a solution of methyl 5-chloromethylthiophene-2-carboxylate (439 mg, 2.30 mmol) in THF (2 mL) was added via cannula and the reaction was allowed to warm to room temperature. After 19 h, TLC analysis showed starting material remained. Another portion of KH (20 mg, 0.50 mmol) was added and the reaction was heated at 50 °C. After 2 h at 50 °C, the reaction was cooled and quenched with 0.5 N HCl (20 mL) and extracted with EtOAc (3 x 25 mL). Combined extracts were washed with brine (50 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (15% EtOAc/Hexane → EtOAc, gradient) afforded 108 mg (19%) of desired product **20**.

Step 2. Oxidative deprotection of **20** to give **21** and **22**

DDQ (91 mg, 0.40 mmol) was added to a mixture of **20** (98 mg, 0.20 mmol) in CH_2Cl_2 (3 mL) and water (0.15 mL). After 4.5 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (15 mL) and extracted with EtOAc (3 x 25 mL). Combined extracts were washed with brine (40 mL) then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by preparative thin layer chromatography (5% MeOH/CH_2Cl_2) afforded 14.4 mg (19%) of alcohol **21** and 16.2 mg (22%) of aldehyde **22**.

Step 3. Grignard reaction with **22** to give the ester of **23**

Pentyl magnesium bromide (2.0 M in Et_2O, 22 μL, 0.044 mmol) was added to a solution of aldehyde **22** (11 mg, 0.029 mmol) in THF (0.2 mL) at –40 °C under nitrogen. After 1.5 h, the reaction was quenched with saturated

aqueous NH_4Cl and extracted with CH_2Cl_2 (3 x 7 mL). Combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by preparative thin layer chromatography (5% MeOH/CH_2Cl_2) afforded 4.8 mg (37%) of the desired ester.

Step 4. Saponification to give **23**

Rabbit liver esterase (134 units/mg, 1 mg) was added to a solution of the ester from step 3 above (3.6 mg, 0.008 mmol) in MeCN (0.1 mL) and pH 7.2 buffer (2.5 mL). After 16.5 h at room temperature, the reaction was diluted with MeCN (7 mL) and concentrated in vacuo. The residue was suspended in CH_2Cl_2 and filtered through a cotton plug. The filtrate was concentrated in vacuo to afford 2.0 mg (57%) of the title compound (**23**).

Example #	Structure	hEP2				hEP4		hFP	hEP1	hEP3	hTP	hIP	hDP
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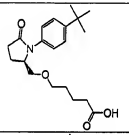
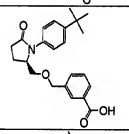
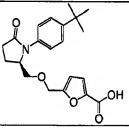
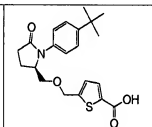
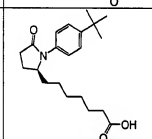
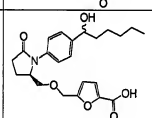
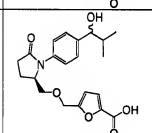
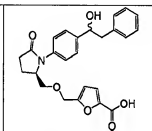
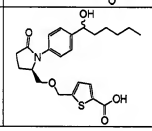
1		>10000				>10000							
2		>10000		NA		>10000	>10000						
3		442	28	4000	189	>10000	>10000	NA	NA	>10000	NA	NA	1921

4		1343	51	501	27	>10000	>10000	NA	>10000	19234	>10000	NA	2323
5		4121	548	>10000		>10000	>10000	NA	>10000	19544	≤10000	NA	>10000
6		388	26	2028		NA	>10000	NA	NA	1927	NA	NA	NA
7		7669	1218	>10000		NA	>10000	NA	NA	NA	NA	NA	NA

8		1228	148	2293		NA	>10000	NA	NA	NA	NA	NA	NA
9		8		115									

Biological Assay Methods

Binding Data

Ki

Competition binding experiments were performed in a medium containing Hank's balanced salt solution, Hepes 20 mM, pH 7.3, membranes (~60 μg protein) or $2x10^5$ cells from HEK 293 cells stably expressing human EP2 receptors, [^{3}H]PGE2 (10 nM) and various concentrations of test compounds in a total volume of 300 μl. Reaction mixtures were incubated at 23 °C for 60 min, and were filtered over Whatman GF/B filters under vacuum. Filters were washed three times with 5 ml ice-cold buffer containing 50 mM Tris/HCl (pH 7.3). Non-specific binding was estimated in the presence of excess unlabeled PGE2 (10 μM). Binding data fitted to the binding model for a single class of binding sites, using nonlinear regression analysis. IC_{50} values thus obtained were converted to Ki using the equation of $Ki=(IC_{50}/(1+[L]/K_D)$ where [L] represents PGE2 concentration (10 nM) and K_D the dissociation constant for [^{3}H]PGE2 at human EP2 receptors (40 nM).

Radioligand Binding

Cells Stably Expressing EP_1, EP_2, EP_4 and FP Receptors

HEK-293 cells stably expressing the human or feline FP receptor, or EP_1, EP_2, or EP_4 receptors were washed with TME buffer, scraped from the bottom of the flasks, and homogenized for 30 sec using a Brinkman PT 10/35 polytron. TME buffer was added to achieve a final 40 ml volume in the centrifuge tubes (the composition of TME is 100 mM TRIS base, 20 mM $MgCl_2$, 2M EDTA; 10N HCl is added to achieve a pH of 7.4).

The cell homogenate was centrifuged at 19000 r.p.m. for 20 min at 4° C using a Beckman Ti-60 rotor. The resultant pellet was resuspended in TME buffer to give a final 1 mg/ml protein concentration, as determined by Biorad assay. Radioligand binding competition assays vs. [^{3}H-]17 –phenyl $PGF_{2\alpha}$ (5 nM) were performed in a 100μl volume for 60 min. Binding reactions were started by adding plasma membrane fraction. The reaction was terminated by the addition of 4 ml ice-cold TRIS-HCl buffer and rapid filtration through glass

fiber GF/B filters using a Brandel cell harvester. The filters were washed 3 times with ice-cold buffer and oven dried for one hour.

[^{3}H-] PGE_2 (specific activity 180 Ci mmol) was used as the radioligand for EP receptors. [^{3}H] 17-phenyl $PGF_{2\alpha}$ was employed for FP receptor binding studies. Binding studies employing EP_1, EP_2, EP_4 and FP receptors were performed in duplicate in at least three separate experiments. A 200μl assay volume was used. Incubations were for 60 min at 25°C and were terminated by the addition of 4 ml of ice-cold 50 mM TRIS-HCl, followed by rapid filtration through Whatman GF/B filters and three additional 4 ml washes in a cell harvester (Brandel). Competition studies were performed using a final concentration of 5 nM [^{3}H]-PGE_2, or 5 nM [^{3}H] 17-phenyl $PGF_{2\alpha}$ and non-specific binding determined with 10^{-5}M of unlabeled PGE_2, or 17-phenyl $PGF_{2\alpha}$, according to receptor subtype studied.

METHODS FOR FLIPR™ STUDIES

(a) CELL CULTURE

HEK-293(EBNA) cells, stably expressing one type or subtype of recombinant human prostaglandin receptors (prostaglandin receptors expressed: hDP/Gqs5; hEP_1; hEP_2/Gqs5; hEP_{3A}/Gqi5; hEP_4/Gqs5; hFP; hIP; hTP), were cultured in 100 mm culture dishes in high-glucose DMEM medium containing 10% fetal bovine serum, 2 mM l-glutamine, 250 µg/ml geneticin (G418) and 200 µg/ml hygromycin B as selection markers, and 100 units/ml penicillin G, 100 µg/ml streptomycin and 0.25 µg/ml amphotericin B.

(b) CALCIUM SIGNAL STUDIES ON THE FLIPR™

Cells were seeded at a density of $5x10^4$ cells per well in Biocoat® Poly-D-lysine-coated black-wall, clear-bottom 96-well plates (Becton-Dickinson) and allowed to attach overnight in an incubator at 37 °C. Cells were then washed two times with HBSS-HEPES buffer (Hanks Balanced Salt Solution without bicarbonate and phenol red, 20 mM HEPES, pH 7.4) using a Denley Cellwash plate washer (Labsystems). After 45 minutes of dye-loading in the dark, using the calcium-sensitive dye Fluo-4 AM at a final concentration of 2 µM, plates were washed four times with HBSS-HEPES buffer to remove excess

dye leaving 100 µl in each well. Plates were re-equilibrated to 37 °C for a few minutes.

Cells were excited with an Argon laser at 488 nm, and emission was measured through a 510-570 nm bandwidth emission filter (FLIPR™, Molecular Devices, Sunnyvale, CA). Drug solution was added in a 50 µl volume to each well to give the desired final concentration. The peak increase in fluorescence intensity was recorded for each well. On each plate, four wells each served as negative (HBSS-HEPES buffer) and positive controls (standard agonists: BW245C (hDP); PGE_2 (hEP_1; hEP_2/Gqs5; hEP_{3A}/Gqi5; hEP_4/Gqs5); $PGF_{2\alpha}$ (hFP); carbacyclin (hIP); U-46619 (hTP), depending on receptor). The peak fluorescence change in each drug-containing well was then expressed relative to the controls.

Compounds were tested in a high-throughput (HTS) or concentration-response (CoRe) format. In the HTS format, forty-four compounds per plate were examined in duplicates at a concentration of 10^{-5} M. To generate concentration-response curves, four compounds per plate were tested in duplicates in a concentration range between 10^{-5} and 10^{-11} M. The duplicate values were averaged. In either, HTS or CoRe format each compound was tested on at least 3 separate plates using cells from different passages to give an $n \geq 3$.

Intraocular Pressure (IOP)

Intraocular pressure studies in dogs involve pneumatonometry performed on conscious Beagle dogs of both sexes (10-15 kg). The animals remain conscious throughout the study and are gently restrained by hand. Drugs are administered topically to one eye as a 25 µL volume drop, the other eye receives 25 µL vehicle (0.1% polysorbate 80:10 mM TRIS) as a control. Proparacaine (0.1%) is used for corneal anesthesia during tonometry. Intraocular pressure is determined just before drug administration and at 2, 4 and 6 hr thereafter on each day of the 5 day study. Drug is administered immediately after the first IOP reading.

The results of the binding and activity studies, presented in Table 1 below, demonstrate that the compounds disclosed herein are selective

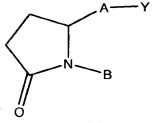
prostaglandin EP_2 agonists, and are thus useful for the treatment of glaucoma, ocular hypertension, inflammatory bowel disease, and the other diseases or conditions disclosed herein.

The foregoing description details specific methods and compositions that can be employed to practice the present invention, and represents the best mode contemplated. However, it is apparent for one of ordinary skill in the art that further compounds with the desired pharmacological properties can be prepared in an analogous manner, and that the disclosed compounds can also be obtained from different starting compounds via different chemical reactions. Similarly, different pharmaceutical compositions may be prepared and used with substantially the same result. Thus, however detailed the foregoing may appear in text, it should not be construed as limiting the overall scope hereof; rather, the ambit of the present invention is to be governed only by the lawful construction of the appended claims.

CLAIMS

What is claimed is:

1. Use of a compound in the manufacture of a medicament for the treatment of inflammatory bowel disease, said compound comprising



or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof; wherein

Y is an organic acid functional group, or an amide or ester thereof comprising up to 12 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 12 carbon atoms; or Y is a tetrazolyl functional group;

A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be substituted with S or O; or A is $-(CH_2)_m-Ar-(CH_2)_o-$ wherein Ar is interarylene or heterointerarylene, the sum of m and o is from 1 to 4, and wherein one CH_2 may be substituted with S or O; and

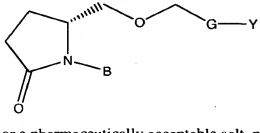
B is aryl or heteroaryl.

2. The use of claim 1 wherein B is phenyl.

3. The use of claim 2 wherein B is alkylphenyl.

4. The use of claim 2 wherein B is *p-t*-butylphenyl.

5. The use of claim 1, said compound comprising

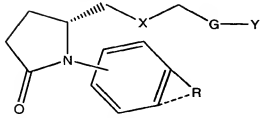


or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof; wherein G is 1,3-interaryl or interheteroaryl, or $-(CH_2)_3-$.

6. The use of claim 6 wherein B is phenyl.

7. The use of claim 7 wherein B is hydroxyalkylphenyl.

8. The use of claim 1, said compound comprising



or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof;

wherein a dashed line indicates the presence or absence of a bond;

R is hydrocarbyl or hydroxyhydrocarbyl having from 1 to 12 carbon atoms;

X is CH_2, O, or S; and

G is 1,3-interaryl or interheteroaryl, or $-(CH_2)_3-$.

9. A compound selected from the group consisting of

5-[(R)-1-(4-*tert*-Butyl-phenyl)-5-oxo-pyrrolidin-2-ylmethoxy]-pentanoic acid;

3-[(R)-1-(4-*tert*-Butyl-phenyl)-5-oxo-pyrrolidin-2-ylmethoxymethyl]-benzoic acid;

5-[(R)-1-(4-*tert*-Butyl-phenyl)-5-oxo-pyrrolidin-2-ylmethoxymethyl]-furan-2-carboxylic acid;

5-[(R)-1-(4-*tert*-Butyl-phenyl)-5-oxo-pyrrolidin-2-ylmethoxymethyl]-thiophene-2-carboxylic acid;

7-[(S)-1-(4-*tert*-Butyl-phenyl)-5-oxo-pyrrolidin-2-yl]-heptanoic acid;

5-{(R)-1-[4-(1-Hydroxy-hexyl)-phenyl]-5-oxo-pyrrolidin-2-ylmethoxymethyl}-furan-2-carboxylic acid;

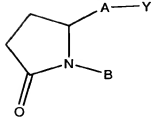
5-{(R)-1-[4-(1-Hydroxy-2-methyl-propyl)-phenyl]-5-oxo-pyrrolidin-2-ylmethoxymethyl}-furan-2-carboxylic acid;

5-{(R)-1-[4-(1-Hydroxy-2-phenyl-ethyl)-phenyl]-5-oxo-pyrrolidin-2-ylmethoxymethyl}-furan-2-carboxylic acid; and

5-{(R)-1-[4-(1-Hydroxy-hexyl)-phenyl]-5-oxo-pyrrolidin-2-ylmethoxymethyl}-thiophene-2-carboxylic acid.

ABSTRACT

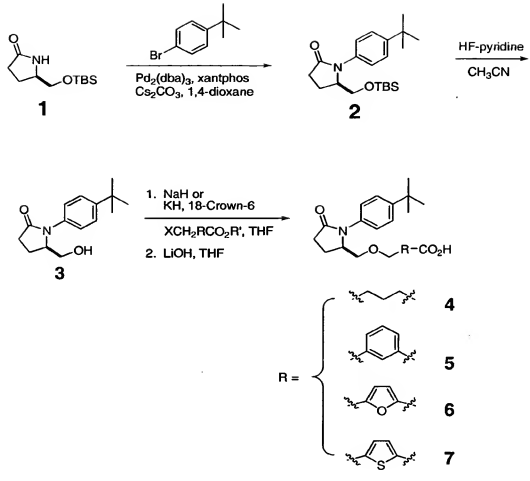
A compound comprising



or a pharmaceutically acceptable salt, prodrug, or a metabolite thereof is disclosed herein. Y, A, and B are as described herein.

Methods, compositions, and medicaments related to these compounds are also disclosed.

Fig. 1



Sheet 1 of 4
Docket 17795 (AP)
SN: Pending
Inventors: Daviw W. Old et al.
Title: Substituted gamma lactams as therapeutic agents
Attorney: Brent A. Johnson, Reg. 51,851
Applicant: Allergan, Inc.

Fig. 2

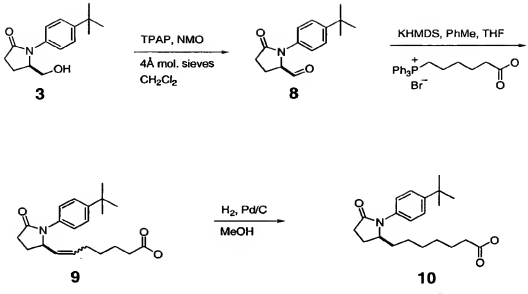

TPAP, NMO
4Å mol. sieves
CH_2Cl_2
KHMDS, PhMe, THF
H_2, Pd/C
MeOH
3
8
9
10

Fig. 3

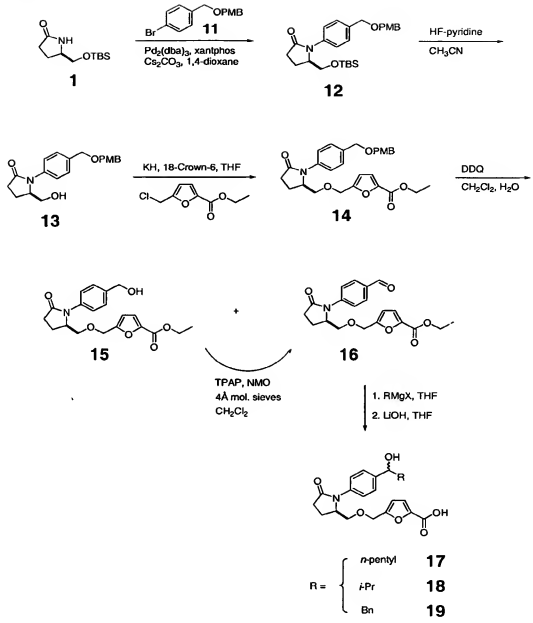
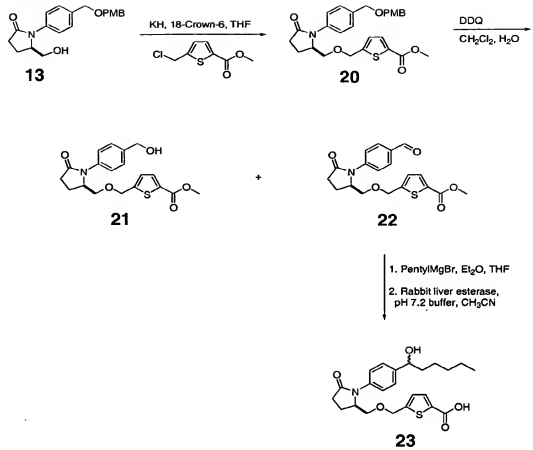

OPMB
Br
11
Pd2(dba)3, xantphos
Cs2CO3, 1,4-dioxane
NH
OTBS
1
OPMB
OTBS
12
HF-pyridine
CH3CN
OPMB
OH
13
KH, 18-Crown-6, THF
Cl
O
O
O
14
DDQ
CH2Cl2, H2O
OH
15
TPAP, NMO
4Å mol. sieves
CH2Cl2
16
1. RMgX, THF
2. LiOH, THF
OH
R
OH
R =
n-pentyl
i-Pr
Bn
17
18
19

Fig. 4


OPMB
OH
13
KH, 18-Crown-6, THF
Cl
S
O
O
OPMB
O
N
O
S
O
O
20
DDQ
CH_2Cl_2, H_2O
OH
21
+
O
22
1. PentylMgBr, Et_2O, THF
2. Rabbit liver esterase,
pH 7.2 buffer, CH_3CN
OH
OH
23

COMBINED DECLARATION & POWER OF ATTORNEY - U.S.A Application

As a below named inventor, I hereby declare that:

My residence post office address and citizenship are as stated below next to my name.

I believe I am the original first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **SUBSTITUTED GAMMA LACTAMS AS THERAPEUTIC AGENTS,** the specification of which

(check one) [X] is attached hereto
[ ] was filed on _____ as US Application Serial Number _____.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability as defined in 37 CFR 1.56. I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

NONE

Prior Foreign Application(s)			Priority Not Claimed
			[ ]
(Number)	(Country)	(Day/Month/Year Filed)	

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below:

(Application Number)	(Filing Date)

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT International application designation the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

NONE

(Application Number)	(Filing Date)	(Status -patented, pending, abandoned)

I hereby appoint **BRENT A. JOHNSON, Registration No. 51,851** (to whom all communications are to be directed), at **Allergan, Inc. (T2-7H), 2525 Dupont Drive, Irvine, CA. 92612, telephone number (714) 246-4348, facsimile number (714) 246-4249,** and the below-named persons (of the same address) individually and collectively my attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and with the resulting patent, with full power to appoint associate attorneys:

Name	Registration No.
Martin A. Voet	25,208
Robert J. Baran	25,806
Stephen Donovan	33,433
Dean G. Stathakis	54,465

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the

United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Signature — Date:

4.	FIRST	M.I.	LAST

Residence/ Post Office Address:

Signature — Date:

5.	FIRST	M.I.	LAST

Residence/ Post Office Address:

Signature — Date: